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Paleoepidemiology of Porotic Hyperostosis in the Libben and Bt-5 Skeletal Populations

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Abstract

The frequencies with which porotic hyperostosis occurred in the Libben Late Woodland (n = 580) and Bt-5 Late Archaic (n = 247) skeletal populations were examined. Aside from temporospatial and cultural affiliations, the skeletal samples representing these two prehistoric band level societies principally differ with respect to level of subadult mortality. That is, juvenile death rates were substantially greater for the Libben group. The goals of the study were to (1) identify those factors which played a paramount role in the etiology of the skeletal lesion in the two groups and (2) evaluate the extent to which porotic hyperostosis serves as a useful bioassay of health status in earlier human groups.

The epidemiological patterns that were observed support the conclusion that Libben and Bt-5 porotic hyperostosis was a fundamental consequence of iron deficiency anemia. In addition, the only significant difference in the frequency of porotic hyperostosis that was observed between the two groups was confined to subadults. Here, Libben children displayed a significantly greater frequency of unremodeled lesions and total lesions compared to those at Bt-5. Evidence is presented which suggests that dietary inadequacy and parasitism played a minor role in the etiology of porotic hyperostosis in the two groups. Alternatively, local environmental circumstances associated with habitation and exploitation of the Black Swamp may have played a fundamental role in elevating infectious disease loads resulting in a greater prevalence of iron deficiency anemia in Libben infants and children compared to those at Bt-5. Factors which contribute to a low level of non-specificity, and age related differences in biological and demographic sensitivity for porotic hyperostosis are discussed.

Introduction

Diseases which become manifest in the human skeleton have piqued the curiosity of physical anthropologists for a considerable period of time. These include both (a) specific and (b) non-specific skeletal and dental lesions. A specific skeletal lesion is one that can be attributed to a single disease entity (eg., multiple myeloma), whereas a non-specific lesion is one that can be induced by a wide variety of disease states and which must therefore be regarded as multicausal. The etiology of a specific skeletal lesion can usually be established with a high level of confidence, and often provide us with information about the health status of a particular individual. However, such abnormalities are infrequent in small human groups. Because of this, specific skeletal lesions provide us with very limited knowledge about the major forces of morbidity and mortality which operated in earlier human groups. The paleoepidemiological utility of specific skeletal lesions is therefore markedly restricted.

Alternatively, non-specific skeletal lesions, though multicausal in nature, are sufficiently frequent to yield epidemiological information on a populational basis. Thus, it is not remarkable that paleoepidemiologists now employ a variety of non-specific indicators of disease and nutritional stress in order to evaluate the potential significance of pathological responses that occurred in earlier human groups. Such responses are presumed to reflect demographic adaptations to diverse and often changing environmental, sociocultural, political, and socioeconomic circumstances. The stress indicators which have been used most frequently include: (1) enamel hypoplasias, (2) enamel hypocalcifications, (3) radiographic evidence of long bone growth perturbations as reflected in Harris lines, (4) patterns of long bone diaphyseal lengths attained at each age, (5) cortical bone remodeling dynamics, and (6) skeletal lesions such as porotic hyperostosis and periosteal reactions (Goodman *et al.*, 1984; Cohen and Armelagos, 1984). It is important to realize, however, that non-specific stress indicators are not of equal paleoepidemiological utility. This is due to the fact that the underlying genetic and environmental factors which interact to determine the phenotypic expression of skeletal and dental stress indicators varies considerably. Thus, each stress indicator is characterized by its own tissue-specific set of benefits and liabilities as a potential bioassay. Skeletal biologists who employ non-specific indicators of disease and nutritional stress to evaluate population fitness in earlier human groups must therefore address two cardinal issues. The first concerns etiology of the stress indicator in question. Thus, in order to identify probable cause of a non-specific lesion on a populational basis, differential diagnoses must be used to evaluate a series of tenable explanatory hypotheses. Those hypotheses which best explain the age and sex specific epidemiological patterns that are observed must then be ascribed greater valence as a source of inference.

The second issue concerns the extent to which a particular population pathology serves as a useful bioassay of disease and/or nutritional stress in earlier human groups. This problem can be approached by examining the demographic sensitivity of our paleoepidemiological tool. Therefore, if a skeletal response is to be regarded as a useful indicator of disease stress, it would be predicted that differences in the age and sex specific frequeney distributions of the lesion will correspond in direction, though not necessarily in magnitude, to differences in age and sex-specific mortality rates that are observed for two or more groups. For those population studies where the relationship between lesion frequencies and mortality rates are found to be discordant, or totally non-existent, then the epidemiological utility of the bioassay must seriously be questioned. In other circumstances the relationship between lesion frequencies and mortality rates may be weak, but nonetheless apparent. Here, we must carefully consider the extent to which potential interpretive value of a lesion outweighs the manifest limitations that characterize such a lesion. Furthermore, in those circumstances where the demographic sensitivity of a particular bioassay is found to be compromised, the paleoepidemiologist must critically evaluate the potential roles that other factors may have played in generating the patterns of lesion distribution that were observed. The latter include various physiological and developmental phenomena, methodological and sampling problems, cultural practices, etc.

Descriptive research in paleopathology has thus far contributed greatly to our knowledge about the distribution, and nature, of diseases that have influenced the course of human evolution in time and space. The primary value of such studies is clearly recognized. However, the view posited here is that paleoepidemiology should be regarded as a subdiscipline of paleodemography, and should not be considered as a parallel, or independent, line of inquiry. Moreover, studies in paleopathology which are not conducted in a demographic context must also be regarded as devoid of evolutionary significance. Thus, it is suggested here that non-specific stress indicators of maximum value will be those which possess three fundamental properties described as follows:

1) The stress indicator should exhibit a high degree of biological sensitivity to one or more environmental perturbations.

2) The stress indicator should be characterized by a high level of demographic sensitivity such that population patterns in the frequency of occurrence

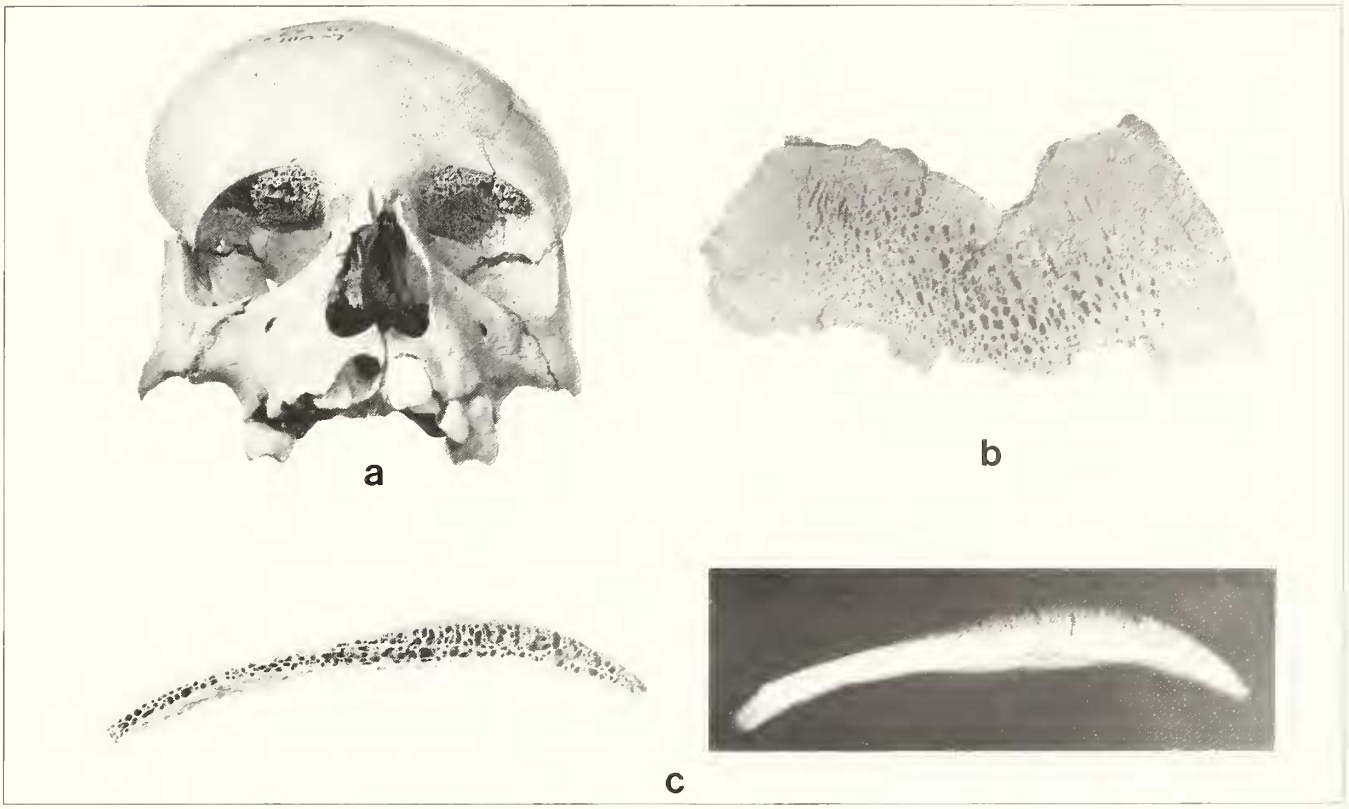

FIGURE 1. *Libben children.* 1a, *Libben child (KSU-08027, 7 years) that displays extensive unremodeled porotic hyperostosis affecting the superior orbital plates.* 1b, *Libben child (KSU-04035, 12-18 months) which exhibits a pronounced unremodeled porotic hyperostotic lesion affecting the right parietal bone fragment. Note the enlarged pore channels enveloped by a well defined microporous cribriform mesh.* 1c, *Shown here are the complimentary photographic and radiographic images of a right parietal bone cross-section. This Libben child (KSU-01258, 3 years) widening of diploic spaces, irregular trabeculation, and the* hair-on-end *striations that are characteristic of erythroid bone marrow hyperplasia.*

of a lesion (i.e., morbidity) can clearly be related to patterns of age and sex specific mortality.

3) The stress indicator should be characterized by a low level of non-specificity. That is, we should be able to infer probable cause of the stress indicator, on a populational rather than individual basis, with a relatively high level of confidence.

Given these perspectives, the purposes of this monograph are to (1) examine in detail the factors which promote the development of erythroid marrow hyperlasia associated anemias in human groups, (2) establish the demographic significance of such anemias in human groups, (3) develop hypothetical model of iron deficiency anemia related porotic hyperostosis that would be expected to occur in earlier human groups, (4) conduct a case study which explores the extent to which this model provides insight with regard to the etiology of porotic hyperostosis as seen in two prehistoric band level societies, and (5) evaluate the demographic sensitivity and paleoepidemiological utility of porotic hyperostosis as a bioassay of population fitness in earlier human groups.

Porotic Hyperostosis in Prehistory

Porotic hyperostosis is a descriptive term for cranial lesions that display a coral, cribriform, or sieve-like porosity (Angel, 1966; Cule and Evans, 1968; El-Najjar, 1975). Common referents for the skeletal lesion that have been reported in the earlier literature include: cribra orbitalia (Welcker, 1888), symmetrical osteoporosis (Hrdlicka, 1914; Williams, 1929), osteoporosis of the cranium (Muller, 1935), cribra cranii (Williams, 1929; Henschen, 1961), and spongy hyperostosis (Putshcar, 1966). The lesions are often symmetrical in disposition, exhibit variable degrees of osseous tissue hypertrophy, and frequently display peripheral hypervascular channels (Hengen, 1971). These skeletal changes are usually visible upon close macroscopic examination (see Figures 1a-c). Radiographic and histological studies of porotic hyperostosis show that the lesions are characterized by irregular trabeculation, widening of diploic spaces, thinning of the endo-and-ectocranial tables (primarily the outer), and a radial pattern of bone spiculation known as *hair-on-end* striations which are oriented perpendicular to the endocranial table of an affected bone (Moseley, 1965;

Greenfield, 1975; El-Najjar and Robertson, 1976).

Porotic hyperostotic skeletal changes can be observed most frequently affecting the anterior portion of the superior orbital plates (Hengen, 1971). Lesions affecting the pericranial surfaces of the frontal, parietal, and occipital bones are more commonly seen in subadults (Carlson *et al.*, 1974). Endocranial skeletal changes tend to be uncommon relative to those which are described above (Henschen, 1961; Hengen, 1971). Severe manifestations of the lesion are accompanied by excessive osseous tissue hypertrophy, obliteration of the outer table, marked resorption and thinning of the inner table, and involvement of temporal, sphenoid, and facial bones (Moseley, 1965).

Skeletal changes that are identical to those described as porotic hyperostosis have been identified in a number of pathological conditions (see Table 1). Radiographic evidence of porotic hyperostosis has been observed most frequently as a consequence of iron deficiency anemia and the chronic hemolytic anemias (Sheldon, 1936; Caffey, 1937; Eng, 1958, Sax, 1963; Baker, 1964; Powell *et al.*, 1965; Aksoy *et al.*, 1966; Lanzkowski, 1968; Agarwal *et al.*, 1970; Shahidi and Diamond, 1960; Britton *et al.*, 1960; Burko *et al.*, 1961; Moseley, 1974; and Williams *et al.*, 1975). The lesions are less frequently seen in association with cyanotic congenital heart disease (Nice, 1964), hereditary spherocytosis (Trucco and Brown, 1967), polycythemia vera (Dykstra and Halberstma, 1940), and pyruvate kinase deficiency (Becker *et al.*, 1971). For all of the conditions listed above the skeletal changes that affect the cranium are the direct result of erythroid bone marrow hyperplasia which occurs in response to an underlying anemic stimulus (Moseley, 1974). Thus, porotic hyperostosis is best considered a non-specific consequence of bone marrow proliferation.

The earliest descriptive reports that identified porotic hyperostosis in prehistoric human groups were published in the late 19th and early 20th centuries (Welcker, 1888; Wood-Jones, 1910; Hrdlicka, 1914; Moore, 1929; Hooton, 1930; and Muller, 1935). Although several hypotheses were posited to explain the skeletal lesion, the pathogenesis of porotic hyperostosis remained vague and enigmatic prior to the mid 1960's (Henschen, 1961; Nathan and Haas, 1966; Angel, 1964; and Moseley, 1965). Historical reviews of the earlier accounts are available in the more recent literature (see El-Najjar and Robertson, 1976; El-Najjar *et al.*, 1976). In general, the earlier studies demonstrated that porotic hyperostosis occurred in skeletal groups of widespread temporospatial distribution, and that the lesions were somewhat more common in populations that had lived in the equatorial regions of the Old and New Worlds.

Currently, two hypotheses are regarded as primary explanations for the etiology of porotic hyperostosis that has been observed in earlier human groups. One considers the lesion to be a fundamental response to some variant of hemolytic anemia that occurred as a consequence of endemic falciparum malaria (Angel, 1966; Zaino, 1964; Ascenzi and Salistreri, 1977). The alternative hypothesis suggests that porotic hyperostosis is a direct result of iron deficiency anemia (Moseley, 1965, Moseley 1966; Hengen, 1971). Historically, both views have been offered to explain the occurrence of porotic hyperostosis in Old and New World skeletal populations alike.

The geographic distribution of the lesion in some areas of the Old World due not conflict with the hemolytic anemia hypothesis (Angel, 1967). However, a substantial

TABLE 1. *List of the Major Clinical Conditions Where Radiographic Evidence of Skeletal Changes in the Cranium Have Been Reported as a Primary Consequence of Erythroid Bone Marrow Hyperplasia*

I. *Congenital Hemolytic Anemias:*
   - A. Thalassemias
     1. Thalassemia Major (i.e., Mediterranean Disease, Cooley's Anemia, Erythroblastic Anemia)
     2. Thalassemia Intermedia - Severe Heterozygous
     3. Thalassemia Minor - Mild Heterozygous
   - B. Sickle Cell Disease
     1. Sickle Cell Anemia (Hemoglobin S-Homozygous)
     2. Hemoglobin C - Homozygous
     3. Hemoglobin E - Homozygous
     4. Hemoglobin S-C
     5. Hemoglobin S - Thalassemia
     6. Other Infrequent Abnormal Hemoglobins
   - C. Hereditary Nonspherocytic Hemolytic Anemias
     1. Glucose-6-Phosphate Dehydrogenase Deficiency
     2. Pyruvate Kinase Deficiency
     3. Other Rare Enzyme Deficiencies
   - D. Hereditary Spherocytosis (i.e., Spherocytic Anemia and Congenital Hemolytic Jaundice
   - E. Hereditary Elliptocytosis (rare)

II. *Iron Deficiency Anemia*

III. *Cyanotic Congenital Heart Disease* (rare)

IV. *Polycythemia Vera in Childhood* (rare)

Adapted from Moseley (1965), The paleopathologic riddle of "symmetrical osteoporosis." *American J. of Roentgenology* 95:135-142.

body of clinical, experimental, and epidemiological research supports the view that iron deficiency anemia played a substantial, if not the major, role in the pathogenesis of porotic hyperostosis in all earlier human groups (Mensforth *et al.* 1978, and references therein). The major proponents of these divergent perspectives, and evidence offered to support such inferences, will thus be considered.

Angel (1967) has favored the view that porotic hyperostosis that is seen in several Old World circum-Mediterranean skeletal groups represents a bony response to the hemolytic anemias of thalassemia and/or sickle cell anemia. The lesion is interpreted to be direct skeletal evidence of balanced polymorphic adaptations which arose in response to the selection pressures of falciparum malaria in pre-modern Old World agricultural communities (Angel, 1966). Evidence given in support of this hypothesis includes geographic distribution and frequency of the lesion in circum-Mediterranean skeletal groups, and overall patterns of cranial and post-cranial skeletal involvement.

For example, the greater incidence of *slight* and *healed* lesions that were observed in these groups are considered to be those skeletal changes which would be expected to occur in thalassemic heterozygotes. Angel (1967) suggested that the low incidence of *severe* porotic hyperostosis was due to an early and intense selection against individuals that were homozygous for the condition. Thus, the marked skeletal changes that are often observed in modern thalassemic homozygotes are attributed to modern medical intervention which has allowed affected individuals to survive for longer periods of time. As a consequence, these individuals are assumed to sustain more pronounced degrees of osseous tissue hypertrophy than would have been the case for pre-modern thalassemic homozygotes. In addition, cortical thinning of the long bones and ribs are cited as post-cranial evidence of erythroid marrow hyperplasia which occurred in response to the hemolytic anemia of thalassemia in these earlier human groups (Angel, 1966; Angel, 1967).

However, some more recent workers concerned with the origin of porotic hyperostosis in Old World circum-Mediterranean archeological populations consider the skeletal evidence for thalassemia to be highly suspect (Ascenzi and Salistreri, 1977). As an alternative, it is suggested that the lesion may be the result of compensatory erythroblastic anemia which occurs in association with malarial infection alone (Germana and Ascenzi, 1980).

The etiology of porotic hyperostosis in New World skeletal groups has likewise been attributed to the hemolytic anemias of thalassemia or sickle cell anemia (Wakefield *et al.*, 1937; Zaino, 1964; Zaino, 1967; Zaino, 1968; Zaino and Zaino, 1969). Evidence in support of this view is weak, and is primarily limited to the observation that a greater incidence, and degree of severity, of the lesion characterizes several New World skeletal groups (for discussion see Moseley, 1965). Angel (1967) considered iron deficiency anemia, primarily as a result of hookworm infestation, to be a more probable cause of porotic hyperostosis in New World populations. Paleoepidemiological research discussed thus far has focused on a general relationship whereby some form of parasitism (i.e., falciparum malaria or hookworm infestation) has been regarded as the principal factor involved in the etiology of porotic hyperostosis that occurred in Old and New World skeletal populations alike.

The major alternative hypothesis is that the majority of porotic hyperostosis that has been observed in human skeletal groups occurred as a result of iron deficiency anemia in direct response to elevated levels of infectious disease and nutritional stress (Moseley, 1965; Moseley, 1966; Hengen, 1971; Carlson *et al.*, 1974; El-Najjar *et al.*, 1975; El-Najjar and Robertson, 1976; El-Najjar *et al.*, 1976; Lallo *et al.*, 1977; Mensforth *et al.*, 1978; Schutte, 1979; Cassidy, 1980; Von Endt and Ortner, 1982; Palkovich, 1985, 1987; Stuart-Macadam, 1985, 1987a, 1987b, 1989; Walker, 1986; Hodges, 1987; Fairgrieve, 1990). Considerable evidence supports this inference. First, contemporary epidemiological studies have demonstrated that iron deficiency anemia is the most common nutritional deficiency that affects human groups on a world-wide basis (Witts, 1966; World Health Organization, 1968; Robbins, 1974; Baker, 1978; Betts and Weidenbenner, 1986). Porotic hyperostosis likewise has a very widespread distribution in Old and New World skeletal populations (Moseley, 1965; Hengen, 1971; El-Najjar *et al.*, 1976; Lallo *et al.*, 1977). Second, the incidence of iron deficiency anemia in modern groups, and the frequency of porotic hyperostosis in skeletal groups, is greater for those populations that subsist (or subsisted) on dietary staples that are low in bioavailable iron (Carlson *et al.*, 1975; El-Najjar and Robertson, 1976; Lallo *et al.*, 1977; Martinez-Torres and Layrisse, 1974; Witts, 1966; Jeliffe and Blackman, 1962; Scrimshaw and Young, 1976; Grantham-McGregor *et al.*, 1974; Burks *et al.*, 1976; and Ashworth *et al.*, 1973). Third, no evidence exists to support the view that any of the hemolytic anemias which arose in response to falciparum malaria in the Old World were operative as selective factors in the pre-Columbian New World (El-Najjar, 1976 and references therein). Nonetheless, hookworm infection most likely contributed to a greater prevalence and incidence of iron deficiency anemia in certain Old and New World human groups (Hengen, 1971).

Benefits and Liabilities of Porotic Hyperostosis Studies

Paleoepidemiological analyses that have employed samples of sufficient size to investigate porotic hyperostosis in earlier human groups have demonstrated a

marked concordance with the iron deficiency anemia hypothesis (El-Najjar, 1976; Lallo *et al.*, 1977; Mensforth *et al.*, 1978; Walker, 1986; Stuart-Macadam, 1989). For example, El-Najjar (1976) examined the frequency of occurrence for porotic hyperostosis in 4,146 individuals from fourteen New World skeletal groups. This macrosample was further subdivided into *maize-dependent* (n=1,722) and *non-maize-dependent* (n=2,424) groups. The rank order frequency of occurrence for porotic hyperostosis in the maize-dependent sample was subadults (31.7%), adult females (25.3%), and adult males (21.6%). Likewise, the rank order frequency of occurrence for porotic hyperostosis in the non-maize-dependent sample was subadults (8.6%), adult females (5.2%), and adult males (2.0%).

Thus, two patterns emerge that are in accord with the iron deficiency anemia hypothesis. First, both subsamples exhibit a rank order frequency of porotic hyperostosis which identifies those age/sex groups at greatest risk of acquiring iron deficiency as a result of intrinsic physiological factors alone. Second, the markedly higher incidence of porotic hyperostosis that characterizes the maize-dependent skeletal groups is a pattern which would be expected to occur as a consequence of diets that are low in bioavailable iron.

However, there are theoretical biases and methodological problems which limit the inferential utility of studies such as the one described above. The first problem concerns the relationship between the frequency of porotic hyperostosis and levels of morbidity and mortality that characterize our comparisons of prehistoric human groups. We may find that one skeletal groups exhibits a frequency of porotic hyperostosis that is statistically significantly greater than another skeletal group. However, differences in lesion frequency alone do not allow us to assess the demographic impact that such disease loads may have had on earlier human groups. That is, if morbidity is high and mortality is low, than many individuals who survive periods of elevated risk would be expected to exhibit lesions that had undergone various stages of healing or remodeling. Alternatively, certain high risk age/sex groups may display elevated frequencies of active lesions at time of death. Thus, before we accept porotic hyperostosis as a useful bioassay of disease and nutritional stress we must first determine whether or not differences in the frequency of the skeletal lesion correlate with differences in mortality rates that are observed. If a positive correlation exists, we must then evaluate the strength of such a relationship. If the relationship is strong, we can then ascribe demographic sensitivity, and evolutionary significance, to the non-specific stress indicator.

The second problem that characterizes many paleoepidemiological inquiries is an over emphasis on dietary hypotheses. Thus, it is routinely assumed that the nutritional status of prehistoric horticultural and agricultural groups will be impaired by the ingestion of domesticated cultigens. It is well recognized that maize, and other Old and New World cereal grains, are low in bioavailable iron and other essential nutrients (Scrimshaw and Young, 1976). However, we often overlook floral and faunal evidence which indicate that many prehistoric horticultural and agricultural groups supplemented their diets with substantial amounts of nutrient rich plant and animal foods that were acquired via foraging, hunting, and/or trade. Furthermore, it is very probable that few prehistoric groups practiced the intense levels of monocropping that occur in many contemporary underdeveloped societies where levels of sanitation and hygiene are poor, population density is high, and the incidence of protein deficiency and protein-calorie malnutrition is exceptionally high (Scrimshaw and Young, 1976; Beisel, 1982; Herbert, 1985; Herbert, 1987).

Perhaps equally important as *diet* are the *demographic* changes that occurred in human groups which made widespread use of domesticated cultigens. Overwhelming empirical evidence has shown that increases in local and regional population densities, combined with the hygiene and sanitation problems of sedentary village life, results in a significant rise in the frequency, duration, and severity of infectious diseases in agricultural communities (Scrimshaw and Young, 1976; Herbert, 1985, and references therein). Moreover, several researchers have documented that half of all nutritional crises are precipitated by infectious disease episodes alone (Gordon *et al.*, 1963; Scrimshaw and Suskind, 1959; Maynard and Hammes 1970; Martorell, 1980). Thus, the extent to which infectious diseases may have contributed to the increased incidence of porotic hyperostosis that occurred in certain prehistoric human groups has not received due consideration in light of its demonstrated importance (Lallo *et al.*, 1977; Mensforth *et al.*, 1978).

The primary methodological problems which limit the utility of many porotic hyperostosis studies are (1) inadequate demographic documentation for the samples being investigated, (2) routine use of broad age intervals for reporting skeletal lesion frequencies, and (3) lack of information about lesion activity status (i.e., active versus healed lesions) at time of death for affected individuals. First, it is important to realize that many human skeletal collections that were assembled during the earlier part of the 20th century are demographically unsound as a result of biased sampling techniques. These include selective recovery of (a) cranial versus post-cranial skeletal remains, and (b) adults versus subadults. Furthermore, the growing interest in human skeletal diseases that fascinated physical anthropologists at the turn of the century may have introduced a further bias

whereby pathological specimens were recovered in greater numbers relative to non-pathological individuals. The extent to which the latter bias may affect many extant human skeletal samples is difficult to assess in retrospect. Nonetheless, it is quite clear that the demographic composition of many skeletal collections is markedly unbalanced. Thus, the quality of age and sex information that has been reported for such materials remains highly suspect (Weiss, 1972; Weiss, 1973; Ruff, 1981).

Second, paleoepidemiologists have often reported skeletal lesion frequencies for very broad, and non-standardized, age groups (i.e., subadults, adult males, and adult females). The use of broad age intervals not only masks useful age-specific patterns in the frequency of occurrence of skeletal lesions, but also masks the effects of census errors. These affects are usually most pronounced for subadults where infant underenumeration can markedly skew the skeletal lesion frequencies that are observed in such groups. Thus, erroneous conclusions about differential health status may arise when skeletal lesion frequencies for demographically balanced skeletal samples are compared to the skewed lesion frequencies of selectively biased skeletal samples. Moreover, the width in years that is used to define the subadult age interval varies from one paleoepidemiological report to the next. Therefore, lesion frequencies that are given for subadults grouped in 0-10 year, 0-15 year, and 0-20 year intervals must be adjusted before meaningful comparisons of health status can be made. However, the information required to carry out such adjustments is all too often lacking in the original reports.

Third, most paleoepidemiological studies make no attempt to discriminate between skeletal lesions that are active versus those which are inactive at time of death. This is peculiar given the fact that unremodeled lesions provide us with our only reasonable estimates of the age-specific frequency of occurrence, and levels of mortality, which may have occurred as a direct, or indirect, result of the disease process which produced the skeletal lesion. The total lesion frequencies most often reported are combined measures of unremodeled and remodeled lesions that were observed in a group. These may provide us with a general index of overall morbidity that accompanied a particular stress indicator. However, combined measures which include remodeled lesions may also introduce a significant amount of noise. That is, our ability to estimate the *real* total frequency with which a skeletal lesion occurred in an earlier human group will be distorted by age progressive bone remodeling. The latter may be further confounded by a sex differential in bone remodeling rates as is the case with Harris lines (see Garn, 1968). In general, these effects will be most pronounced in adults where the (a) frequency of unremodeled lesions that are observed is likely to be lower than the frequency of total lesions that are observed, and (b) the frequency of total lesions that are observed is likely to be lower than the frequency of total lesions that occurred in the group.

Significance of the Iron Deficiency Anemia Hypothesis

Contemporary epidemiological surveys have shown that iron deficiency anemia is so common in human groups throughout the world that the prevalence of iron deficiency is now regarded as one of the best indices of the nutritional health status of a population (Witts, 1966; World Health Organization, 1968; Kilpatrick, 1970; Baker, 1978; Wenguang *et al.*, 1986). The biological significance of iron resides in the fact that it is required to sustain important physiological processes. These include hemoglobin synthesis, tissue respiration, enzyme activity, and oxidative-reduction reactions (Macdougall *et al.*, 1975). Iron also plays a paramount role in the maintenance of host immunological competence (Prasad, 1979), and the maintenance of normal epithelial tissue structure and function (Naiman *et al.*, 1969). Furthermore, studies have shown that an individual's ability to maintain adequate body tissue iron stores and dietary absorption of the nutrient are directly related to health status (World Health Organization, 1968 and references therein). Therefore, the intrinsic physiological and extrinsic environmental factors that are involved in the etiology of iron deficiency anemia will be considered.

Intrinsic Physiological Risk Factors that Elevate Risk of Iron Deficiency Anemia

Clinical studies have shown that iron deficiency anemia occurs most frequently in those age and sex groups of a population where physiological demands for the nutrient are greatest (Heath and Patek, 1937; Hallberg *et al.*, 1970; Robbins, 1974; Olivares *et al.*, 1986). Thus, four high risk groups can be identified in any human group. These can be further subdivided into two major and two minor high risk groups. The two groups at greatest risk of acquiring iron deficiency anemia are (1) infants and young children that range in age from 6 months to three years, and (2) adult females in their child-bearing years (Finch, 1968a, and 1968b). The two minor high risk groups are (1) adolescent males and females, and (2) men and women over 60 years of age (Scott *et al.*, 1970).

Birthweight and rate of somatic growth are now recognized as the two most important constitutional factors which elevate the risk of iron deficiency anemia in infants and young children (Josephs, 1956; Jacobs and Wormwood, 1982; Laskari, 1984; Betts and Weidenbenner, 1986). Infants are born with iron concentrations that are proportional to body weight, and iron stores established at birth are the most important source of the nutrient for the first six months of life (Mackay, 1931; Mackay, 1933).

Indeed, in otherwise healthy full-term infants a rapid rate of somatic growth alone often results in significant tissue iron depletion by six months of age (Josephs, 1956). Thereafter, exogenous sources of iron are required in order to meet the infant's physiological demands for the nutrient.

Thus, it is not remarkable that the combined effects of (1) rapid somatic growth, (2) frequent infections, and (3) weaning diets of poor nutritional quality often give rise to a high frequency of iron deficiency anemia in infants and young children (Josephs, 1936; Josephs, 1953; Betke, 1970; Smith, 1972; Scrimshaw and Young, 1976). In modern well-nourished societies pediatricians often consider iron deficiency anemia in infants to be a transitional *state* in which the child is more anemic than ill (Sturgeon, 1956; Betke, 1970; Smith, 1972; Thomas *et al.*, 1977). In developing countries, however, the condition is often much more prevalent, severe, and contributes significantly to elevated levels of subadult morbidity and mortality (Akel *et al.*, 1963; Manchandra *et al.*, 1969; Maynard and Hammes, 1970; Ashworth, 1973; Grantham-McGregor *et al.*, 1974; Burks *et al.*, 1976).

With regard to adult females, pregnancy is the major physiological circumstance that elevates risk of acquiring iron deficiency anemia (Witts, 1966; Yusufji *et al.*, 1973). Population studies have reported a world-wide prevalence of nutritional anemias in pregnancy that range between fifteen and ninety-nine percent (Witts, 1966; World Health Organization, 1968; Finch *et al.*, 1968; Scott *et al.*, 1970). Hunter's (1960) survey of nutritional anemias in pregnancy further showed that ninety-eight percent were the direct consequence of iron deficiency, with folate and B_{12} deficiencies occupying a minor role in overall etiology.

The important intrinsic factors which interact to increase the risk of iron deficiency anemia during pregnancy include (1) low tissue iron stores at the onset of pregnancy due to the cumulative effects of regular menstrual iron losses, (2) the physiologic hydremia of pregnancy where expanding plasma volume has the net effect of decreasing maternal hemoglobin concentration, packed red cell volume, and red cell count, (3) maternal excretion of iron in urine and sweat, (4) fetal and placental iron requirements, and (5) blood loss at parturition (Finch, 1968a; Finch, 1968b; Pritchard and Scott, 1970).

More specifically, the third trimester fetal iron demands are so great that maternal tissue iron stores rapidly become depleted (Yusufji *et al.*, 1973). At this time maternal iron balance becomes highly dependent upon dietary absorption which may increase three to four times above normal in order to meet excessive maternal and fetal iron requirements (Apte and Iyengar, 1970). These observations are concordant with the finding that iron deficiency anemia in pregnant women is most prevalent during the third trimester (Yusufji *et al.*, 1973). In addition, the period of lactation following parturition is accompanied by additional iron requirements that amount to 0.5-1.0 mg. iron per day above the normal 1.5 mg. of iron per day that is normally absorbed from the diet (Finch, 1968a; Finch, 1968b).

Among the two minor population age/sex groups that are at elevated risk of acquiring iron deficiency anemia, the principal risk factor in adolescents is accelerated rate of somatic growth (Saddi and Schapira, 1970; Kenney, 1985; Liebman, 1985). The increased tissue iron requirements that accompany the adolescent growth spurt can rapidly deplete body iron stores and establish a latent iron deficient state. In addition, the onset of menarche and subsequent menstrual blood losses contribute to a sex differential whereby adolescent females experience a higher incidence of iron deficiency anemia relative to males (Rybo, 1970; Saddi and Schapira, 1970). Finally, individuals of both sexes that are over sixty years of age are at elevated risk of developing iron deficiency anemia due to age progressive degeneration in the absorptive capacity and efficiency of the gastrointestinal tract (Finch, 1968a; Finch, 1968b).

Extrinsic Factors Which Elevate Risk of Iron Deficiency Anemia

Diet.—The absorption of dietary iron is dependent upon the bioehemical properties of food items that are ingested, and the organism's physiological controls which are designed to maintain a conservative equilibrium (Conrad, 1970; Davis, 1970). In humans, iron is absorbed primarily in the duodenum, the most alkaline portion of the gastrointestinal tract (Davis, 1970). In order to meet nutritional requirements, iron must be exposed to the mucosa of the small intestine in a soluble state, in reasonable quantities, and for a sufficient length of time (Conrad, 1970). Under normal circumstances the body exerts rigid control over iron homeostasis through conservation, reutilization, and by regulating the processes by which iron losses are replenished (Conrad, 1970). For example, healthy infants absorb approximately ten percent of available dietary iron (Heinrich, 1970). In contrast, iron deficient infants have the capacity to absorb two to three times the normal amount as a means of compensating for iron loss and tissue iron depletion (Andelman and Sered, 1966; Saddi and Schapira, 1970).

Studies concerned with the bioavailability of dietary iron have demonstrated that the iron content of food varies tremendously (Wretlind, 1970; Martinez-Torres and Layrisse, 1974; Morck *et al.*, 1981; Palazzari *et al.*, 1986). Even among similar food items the iron content may vary depending on how the food is prepared and, for vegetable food items, where it is grown (Bressani, 1958; Cook and Monsen, 1976). For example, heme iron is more readily absorbed than ferrous iron, and the latter is better absorbed than ferric iron (Callender *et al.*, 1957; Hallberg and

Sovell, 1967; Turnbull *et al.*, 1967). Also, meat products generally contain more iron that is in a readily absorbable form (Layrisse *et al.*, 1968; Layrisse *et al.*, 1969; Martinez-Torres and Layrisse, 1971).

The bioavailability of iron is also dramatically influenced by other dietary constituents such as chelating agents (Hwang and Brown, 1965; Kuhn *et al.*, 1968; Davis, 1970). These compounds can either promote or inhibit iron absorption. Ascorbic acid is a chelating agent which promotes iron absorption by producing a water soluble iron complex (Moore *et al.*, 1940). Several sugars and amino acids also facilitate iron absorption by decreasing the precipitation and polymerization of dietary iron (Charley *et al.*, 1963; Pollack *et al.*, 1964; Martinez-Torres and Layrisse, 1970). In contrast, compounds such as phytates, phosphonates, carbonates, and oxylates strongly inhibit the absorption of dietary iron by effectively binding iron into insoluble macromolecules (Hegsted *et al.*, 1949; Sharpe *et al.*, 1950; Foy *et al.*, 1959; Hussain and Patwardhan, 1959; Conrad, 1970).

Qualitatively superior and inferior dietary regimens have been reported in association with iron deficiency anemia in children (Davidson *et al.*, 1935; Josephs, 1956; Dawson and Desforges, 1958; Woodruff, 1958). In general, a consistent relationship between anemia and artificial, or prolonged, milk feeding has been demonstrated in modern groups (Mackay, 1931; Fullerton, 1937; Smith, 1972). Epidemiological studies have also confirmed that prolonged breast feeding and weaning diets of maize or corn gruels often occur in association with a high incidence of iron deficiency anemia in infants and young children (Ashworth, 1973; Jelliffe and Blackman, 1962; Grantham-McGregor *et al.*, 1974). These findings are attributed, in part, to the high phosphorous content in milk and corn, as well as the high concentration of phytic acid in corn, which inhibits the absorption of dietary iron (Lanzkowski and McKenzie, 1959; Martinez-Torres and Layrisse, 1974).

Another factor to be considered with regard to nutritional status, in infants and children in particular, is the extent to which acute and chronic gastrointestinal infections lead to the malabsorption of dietary iron and other essential nutrients (Conrad, 1970; Carpenter and Sack, 1981; Gryboski and Walker, 1983; Santos, 1986). Diarrheal episodes promote malabsorption by increasing intestinal motility (Gordon *et al.*, 1963; Fagundes-Netto, 1984). Therefore, both the quantity of iron and the amount of time that it is made available to the absorptive surfaces of the intestinal tract are decreased. In addition, diarrheal episodes are accompanied by dehydration, electrolyte imbalance, negative nitrogen balance, loss of appetite, and the substitution of solid foods by starchy gruels of lower nutritional quality (Gordon *et al.*, 1963; Scrimshaw, 1964). Moreover, tissue iron depletion alone appears to be an important factor which promotes malabsorption syndrome in iron deficient individuals (Naiman, 1969).

Severe degenerative epithelial tissue changes (i.e., glossitis, stomatitis, and koilonychia) are not commonly observed in iron deficient adults unless the condition persists for an indefinite period of time (Halsted *et al.*, 1965; Yusufji *et al.*, 1973). However, iron deficient infants and children are reported to experience a relatively high incidence of gastrointestinal dysfunction that results in malabsorption syndrome (Hawksley *et al.*, 1934; Wilson *et al.*, 1962; Halsted *et al.*, 1965; Guha *et al.*, 1968; Naiman *et al.*, 1969). Tissue iron depletion alone is a major factor responsible for defects in epithelial tissue structure and function that occurs in iron deficient children (Naiman *et al.*, 1969). The most important cytological defects include: atrophy of the gastric and duodenal mucosa, diminished synthesis and secretion of gastric acid, and reduced gastrointestinal enzyme activity (i.e., mucosal disacharidase and cytochrome oxidase activity) (Guha *et al.*, 1968; Halsted *et al.*, 1965; Mahoney and Hendricks, 1975).

Atrophy of the gastric mucosa is usually the most frequent and pronounced tissue change that occurs in iron deficient children (Davidson and Markson, 1955; Badenoch *et al.*, 1957; Rawson and Rosenthal, 1960). The functional consequence of atrophic gastritis is a reduction in gastroferrin synthesis and gastric acid secretion (Stewart, 1937; Shearman *et al.*, 1966; Ghosh *et al.*, 1972; Smith, 1972). The latter abnormality has important implications for those individuals who already exist in an overt state of iron deficiency. Under normal circumstances gastric acidity promotes the absorption of dietary iron and calcium by preventing the formation of insoluble macromolecules (Cook *et al.*, 1964; Mahoney and Hendricks, 1975). The altered gastric pH which occurs more commonly in iron deficient children exacerbates the circumstance by further reducing the amount of dietary iron that is available to the host in a soluble form which can readily be absorbed in the duodenum.

Gastric mucosal atrophy also effects erythropoiesis by interfering with the synthesis and secretion of intrinsic factor (Guyton, 1976). This compound is produced by parietal cells of the gastric mucosa and plays a significant role in facilitating the absorption, and preventing the digestion, of vitamin B_{12} in the intestinal tract. Vitamin B_{12} is required for red blood cell maturation. In the absence of intrinsic factor vitamin B_{12} absorption is impaired. The process of hemoglobin synthesis is not affected, but a macrocytic anemia is a common consequence (Guyton, 1976).

Though less pronounced, atrophy of the duodenal mucosa and reduced enzyme activity of the small intestine promotes the malabsorption of fats, some carbohydrates, and contributes to occult blood loss in iron deficient subjects (Wilson *et al.*, 1962; Naiman *et al.*, 1969). Furthermore, iron deficiency anemia in children is regarded

as one of several protein-losing enteropathies (Lahey, 1962). Pathological effects include malabsorption of dietary amino acids and leakage of plasma proteins in the GI tract. Thus, cytological damage to the GI tract which occurs in iron deficient children has a negative impact on nutritional status in general, and further reduces the bioavailability of dietary iron at a time when physiological demands for the nutrient are great.

Infectious disease: impaired immune response and nutritional immunity.—The synergistic relationships between iron deficiency anemia and infectious disease has received considerable attention in recent years. Clinical and experimental studies have repeatedly demonstrated that iron deficient humans and laboratory animals experience a greater incidence and severity of infectious disease episodes compared to normal healthy subjects (Shaw and Robertson, 1964; Werkman *et al.*, 1964; Kilpatrick, 1970; Baggs and Miller, 1975). In humans, this relationship is particularly marked for children under five years of age (Andelman and Sered, 1966; Arbeter *et al.*, 1971; Joynson *et al.*, 1972; Chandra, 1973; Chandra and Saraya, 1975; Macdougall *et al.*, 1975; Scrimshaw and Young, 1976; Krantman *et al.*, 1982; Chandra, 1985; Walter *et al.*, 1986). Indeed, the high incidence of respiratory and gastrointestinal infections that occur in iron deficient infants and children significantly contribute to growth retardation and elevated levels of subadult morbidity and mortality in many contemporary under-developed societies (Witts, 1966; Gordon *et al.*, 1967; Jose and Welch, 1970; Maynard and Hammes, 1970; Krantman *et al.*, 1982; Forman *et al.*, 1984; McMurray, 1984; Hercberg *et al.*, 1986). Thus, the interactions of anemia and infection have important demographic consequences for populations that are subjected to intensified levels of disease and nutritional stress.

One of the most significant findings in recent years concerns the fact that impaired immune response in an early manifestation of tissue iron depletion (Chandra, 1973, 1985; Macdougall *et al.*, 1975; Prasad, 1979). The principal implication is that host resistance to infectious disease is compromised prior to the onset of overt iron deficiency anemia. Studies have shown that both (1) cell mediated immunity and (2) bactericidal capacity of leukocytes are suppressed in iron deficient subjects (Arbeter *et al.*, 1971; Macdougall *et al.*, 1975; Srikantia *et al.*, 1976; Weinberg, 1977; Root and Cohen, 1981). Though similar defects in immune response occur in protein-calorie malnutrition, the site of the biochemical defect in iron deficiency differs and does not appear to be directly related to protein deprivation (Macdougall *et al.*, 1975; Purtillo and Connor, 1975; Bhaskaram and Reddy, 1975; Bhaskaram *et al.*, 1977; Prasad, 1979; Hoffman-Goetz and Kluger, 1979; Chandra and Au, 1980; Gross and Newberne, 1980).

Suppressed leukocyte function in iron deficient subjects is a direct consequence of tissue iron depletion (Chandra, 1973, 1985). One proposed defect involves myelo-peroxidase (MPO) synthesis (Baggs and Miller, 1975; Yetkin *et al.*, 1979; Parry *et al.*, 1981). MPO is an enzyme that is dependent on heme iron for its activity. It plays a substantial role in the metabolic pathway that mediates the phagocytic capacity of polymorphonuclear (PMN) leukocytes. Simply stated, certain phagocytic cells of the mammalian reticuloendothial system (i.e., eosinophils, neutrophils, and macrophages) require MPO to synthesize hydrogen peroxidase. The latter enzyme is involved in the intracellular processes of lysosomal pathogen killing (Baggs and Miller, 1975). The reduction in leukocyte MPO concentrations, and the subsequent decrease in leukocyte bactericidal activity, appears to be a major factor contributing to the high incidence and greater severity of infections that have been observed in iron deficient children (Arbeter *et al.*, 1971; Macdougall *et al.*, 1975).

Recent research has also demonstrated that reduced quantities of the iron-containing enzyme ribonucleotide reductase, and other cytochrome heme enzymes, impair DNA and protein synthesis in iron-deficient subjects (Joynson *et al.*, 1972; Jacobs and Joynson, 1974; Beisel, 1982). The resultant effects include suppressed (a) lymphocyte production, (b) cytotoxic T lymphocyte activity, and (c) neutrophil ferritin and lactoferrin production (Prasad, 1979; Root and Cohen, 1981; Beisel, 1982; Kuvibidila *et al.*, 1981, 1983a, 1983b; McMurray, 1984). Thus, impaired immune response is a direct, and early, consequence of tissue iron depletion that compromises host resistance to infectious disease.

In addition, the competitive relationship between host and microbe iron requirements, and the subsequent host response to infectious episodes, can substantially reduce the amount of iron that would normally be available to the host for the maintenance of physiological processes. It is now well recognized that iron is a prime nutrilite that is required by bacterial and viral pathogens in order to survive and multiply in mammalian host tissues (Brendstrup, 1950; Weinberg, 1966; Weinberg, 1974). Moreover, many pathogens have evolved the capacity to synthesize and secrete siderophores (Weinberg, 1966; Garibaldi, 1972; Weinberg, 1977; Kochan, 1977b). These are iron-binding compounds which enable the microbe to compete effectively with host iron-binding proteins and host tissues for essential iron (Weinberg, 1977 and references therein). Studies have demonstrated that both the (1) rate of growth and (2) virulence of bacterial pathogens are directly related to the amount of free iron that is available to the microbes (Martin *et al.*, 1963; Shade, 1963; Kaye and Hook, 1963; Brubaker *et al.*, 1965;

Weinberg, 1966; Bullen and Rogers, 1968; Polk and Miles, 1971; Kochan, 1977a, 1977b, 1978; Kluger and Rothenburg, 1979; Hoffman-Goetz *et al.*, 1981; Hoshishima *et al.*, 1985).

Under ordinary circumstances, iron-binding proteins play a critical role in regulating the amount of free iron that is available to pathogens (Weinberg, 1974). Serum proteins such as transferrin, and large concentrations of lactoferrin contained in human breast milk, exert a strong bacteriostatic effect on microbial growth (Bullen and Rogers, 1968; Bullen *et al.*, 1968; McFarlane *et al.*, 1970; Fletcher, 1971; Bullen *et al.*, 1972; Hanson and Winberg, 1972; Purtillo and Connor, 1975; McFarlane, 1976; Faulk, 1976). This bacteriostatic effect is greatly diminished, or completely abolished, in individuals with severe protein deficiency where cause of death is most often due to overwhelming infections (McFarlane and Hamid, 1973). Iron-binding proteins are therefore considered to be an important non-specific factor in host resistance to infectious disease.

The hypoferremia which is induced by host response to local and systemic infections also plays a key role in iron economy (Grieger and Kluger, 1978). It has long been recognized that infectious disease episodes are accompanied by a dramatic reduction in serum iron concentrations (Cartwright *et al.*, 1946; Greenberg *et al.*, 1947; Kuhns *et al.*, 1950). This effect is mediated by plasma transferrins which bind free iron and store it in the reticuloendothelial system (i.e., liver, spleen, and bone marrow) for the duration of the infection (Cartwright *et al.*, 1946; Vannotti, 1957; Kochan, 1978). The physiological response whereby the host induces a hypoferric state in an attempt to deprive the pathogen of necessary iron has been termed *nutritional immunity* by Weinberg (1974). Therefore, iron which would normally be mobilized for hemoglobin synthesis is sequestered from both host and pathogen for the duration of the infectious episode.

Mild infections of short duration usually have no significant effect on hemoglobin levels in adults (Kuhns *et al.*, 1950; Chandra, 1985). If the infection persists a normochromic normocytic, or slightly hypochromic microcytic, anemia can develop. This is commonly referred to as the anemia of infection (Cartwright *et al.*, 1946). However, among infants and children both mild and severe, acute and chronic, infections can result in a marked decrease in hemoglobin levels (Mackay, 1933; Davidson and Fullerton, 1938; Manchandra *et al.*, 1969). In effect, erythropoiesis is suppressed and hemoglobin synthesis is markedly inhibited (Cartwright *et al.*, 1946). Furthermore, the regain of normal erythropoietic activity following recovery from an infectious episode can be delayed for several weeks to several months in young children (Fullerton, 1937). Thus, respiratory and gastrointestinal tract infections that occur during periods of rapid growth can interfere with the bioavailability of iron and precipitate, or exacerbate, an iron deficient state. Iron deficiency anemia may ensue even though the amount of iron available in the diet is more than adequate.

Some clinical researchers have challenged the concept of *nutritional immunity* and have questioned the adaptive significance of hypoferremia due to infectious episodes (Srikantia *et al.*, 1976; Prasad, 1979). These researchers emphasize the fact that impaired immune response is an early consequence of tissue iron depletion. It is argued that a hypoferric state would further compromise immunological competence of the host. However, these investigators have failed to consider that during infectious episodes iron, particularly heme iron, is diverted to those tissues of the immune system, the reticuloendothelial system (RES), which require it most in order to maintain, or enhance, cell-mediated immunity, phagocytic activity, and the bactericidal capacity of PMNs.

Studies have shown that infections inhibit RES erythropoietic activity and hemoglobin synthesis (Kuhns *et al.*, 1950 and references therein). At the same time, however, infections stimulate RES myeloid tissues (Cartwright *et al.*, 1946; Smith, 1972). The implication is as follows. Although heme iron may not be available for hemoglobin synthesis, it may well be used to promote protein synthesis, lymphocyte production and cytotoxic competence, and leukocyte phagocytic activity and bactericidal capacity (Vannotti, 1957; Kochan, 1978). Viewed in this perspective, host response to infectious disease (i.e., hypoferremia) and its subsequent effects on the differential bioavailability of iron appear to be complimentary physiological adaptations.

Cultural practices and parasitism.—In addition to constitutional factors, diet, and microbial infection, a number of cultural and environmental variables are also known to play a role in the etiology of iron deficiency anemia (Shah and Seshadri, 1985). For example, Gordon and associates (1963) have shown that (1) culturally prescribed weaning practices and (2) age and sex specific food restrictions and/or taboos, may contribute to patterns of chronic malnutrition in certain human groups. Likewise, an important environmental variable in tropical and subtropical regions of the world is parasitic hookworm infestation (Roche and Perez-Gimenez, 1959; Bradfield *et al.*, 1968; Venkatachalam, 1968). This promotes intestinal blood loss which can lead to chronic iron deficiency anemia in some individuals.

With respect to trends in morbidity and mortality, it is worthy of comment that adults and subadults generally tolerate uncomplicated iron deficiency anemia rather well. In children the anemic condition may further operate as a

homeostatic mechanism that functions to balance iron metabolism during developmental periods of fluctuating supply and demand. Such a physiological homeostat has a strong selective value for rapidly growing organisms that must constantly balance iron economy with respect to (1) nutritional requirements and bioavailability on the one hand, and (2) host *nutritional immunity* in response to infectious diseases on the other. Arbeter and associates (1971) have expressed a similar view with respect to the iron deficiency anemia that accompanies protein deficiency. These workers suggest that the anemia may be an adaptation to the lowered metabolism of protein-deprived tissues.

The epidemiological relationships discussed thus far can be summarized as follows:

1) Although prevalence may vary, iron deficiency anemia occurs in all human groups, and is the single most common nutritional disorder that affects humans on a world-wide basis.

2) Intrinsic physiological risk factors play a major role in predisposing certain age/sex groups to iron deficiency anemia. The age/sex groups at greatest risk are infants and young children six months to three years of age, and adult females in their peak period of fertility. Those age/sex groups at lesser risk are adolescents, females in particular, and elderly individuals.

3) Infants and young children represent those individuals at greatest risk of elevated morbidity and mortality as a consequence of physiological dysfunctions accrued in association with iron deficiency anemia. These include impaired immune response and malabsorption syndrome which may occur as a result of marked tissue iron depletion alone.

4) The prevalence of iron deficiency anemia is sensitive to differences in extrinsic environmental factors that vary in human groups. Thus, a high incidence of iron deficiency anemia has repeatedly been observed in societies that (a) subsist on diets low in bioavailable iron, and (b) experience elevated levels of infectious diseases.

Thus, it is clear that iron deficiency anemia has a measurable impact on the health status and demographic characteristics of extant human populations. Similarly, if porotic hyperostosis in earlier human groups occurred as a primary consequence of iron deficiency anemia, it would be reasonable to infer that strong demographic correlates exist which argue in favor of the skeletal lesion's utility as a bioassay of disease and nutritional stress.

Hypothetical Model of Skeletal Lesion Differential Sensitivity

Paleoepidemiologists are clearly aware that hematological data on the living provide the most accurate, and sensitive, measure of the prevalence, morbidity, and mortality associated with iron deficiency anemia in extant human groups. Skeletal lesions, by comparison, must always be regarded inferior with respect to their ability to assay such conditions in extinct human societies. The extent to which a skeletal lesion conforms to predicted patterns of a particular disease age/sex distribution will thus strongly influence the degree to which such lesions provide information useful for generating inferences about the health status of earlier human groups.

With regard to the property of sensitivity, Figures 2a-c illustrate the lesion frequency distributions which would be expected for a hypothetical skeletal response that exhibited high sensitivity, low sensitivity, differential sensitivity based on age and/or sex, and no sensitivity to a hypothetical disease and/or nutritional stress identified here as *Disease X*. For this simple model let us assume that (a) no sex differences characterize *Disease X*, (b) three discrete age groups are at risk, and (c) those at greatest risk are subadults, those at moderate risk are adolescents, and those characterized by a lower risk are middle aged adults. For this model the magnitude of *Disease X* is irrelevant. Hence, frequency can represent the number of individuals affected for a designated radix, or frequency can simply refer to the percent of individuals affected at each age where age is in years. Here, we are only concerned with the extent to which our fictive skeletal lesion mimics the epidemiological pattern of the hypothetical disorder.

Relative to the epidemiological distribution of *Disease X*, as measured by modern clinical techniques, Figure 2a identifies skeletal lesion frequencies that display high sensitivity (dot screen), and low sensitivity (black screen), to the disorder. Nonetheless, in each case the pattern of lesion distribution corresponds well with that of *Disease X*, and correctly identify those age groups at risk and the differential magnitude of such risk. Figure 2b illustrates the circumstance where a skeletal lesion displays differential age-related sensitivity. Here, the fictive skeletal response (dot screen) provides a poor assay of the frequency with which *Disease X* affected subadults and middle aged adults. Nonetheless, the skeletal lesion provides a useful index of the extent to which *Disease X* affected adolescents in the population. Finally, Figure 2c illustrates the circumstances where the skeletal lesion itself may be either frequent (dot screen) or infrequent (black screen), but in each case the pattern of lesion distribution bears no relationship to the underlying epidemiological profile of *Disease X*.

With respect to various non-specific skeletal and dental indicators of disease and nutritional stress that are currently

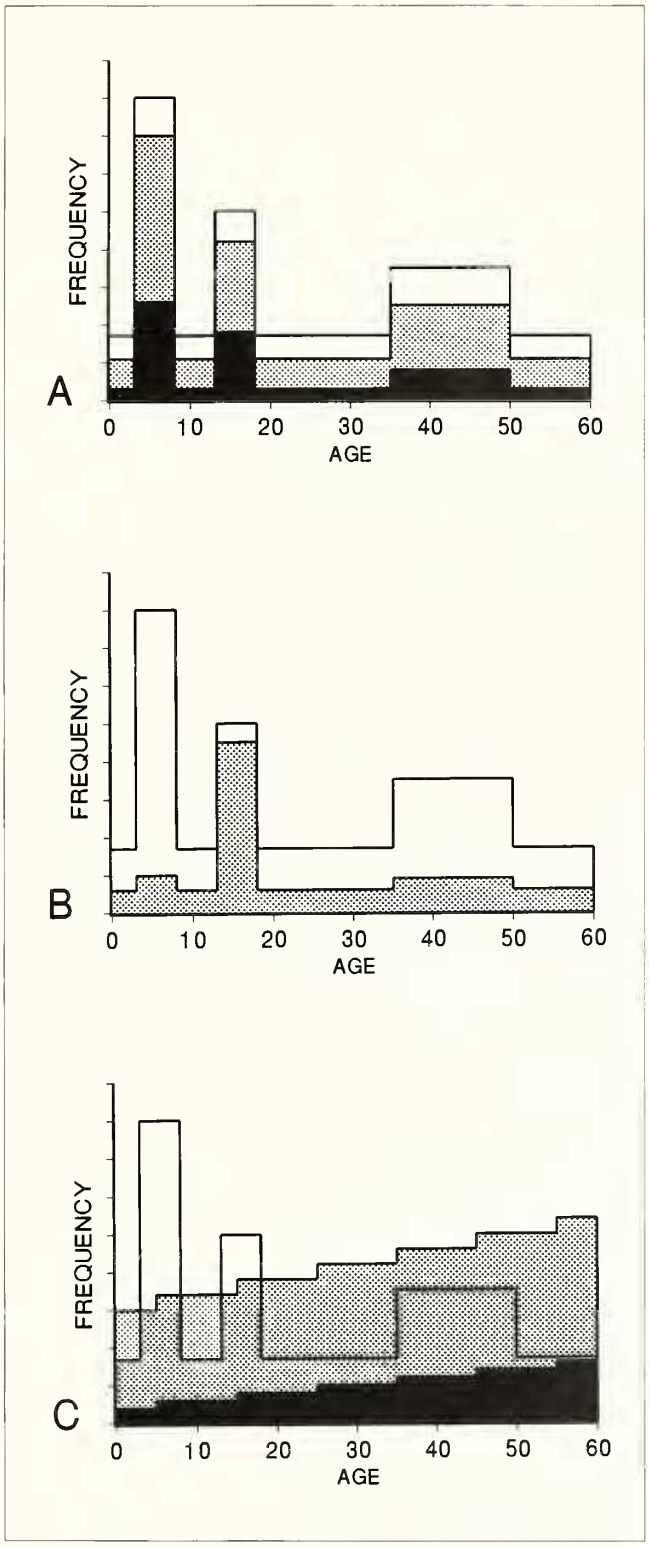

FIGURE 2. *Hypothetical models of differential skeletal lesion responsiveness to a hypothetical clinical disorder (i.e., disease or nutritional stress). Shown in* 2a *is the pattern we would expect to observe for a skeletal lesion that displayed high fidelity where age groups at risk are clearly identified. The dot screen distribution portrays a lesion of high sensitivity to the underlying disorder, whereas the black-screen distribution indicates a low sensitivity (i.e., infrequent) lesion pattern. Model* 2b *illustrates a skeletal lesion (dot-screen) that exhibits differential age-related sensitivity to clinical* Disease X. *Here, the skeletal lesion is sensitive to, and provides a useful bioassay of, the disease as it affects adolescents. However, the lesion pattern is relatively insensitive to the frequency with which* Disease X *affects subadults and middle aged adults. Model* 2c *illustrates skeletal lesions which are both common (dot-screen) and uncommon (black-screen). However, neither pattern of skeletal lesion distribution corresponds with the epidemiological profile of* Disease X. *Skeletal lesions such as these (i.e., those which are insensitive to the underlying clinical disorder) must be regarded as poor, or useless, bioassays of health status in earlier human groups.*

in use, it is clear that many factors may synergize to generate one, or more, of the patterns illustrated above, compromise their sensitivity as a bioassay, and restrict their epidemiological utility. Primary among these are (1) tissue-specific rates of growth, development, maturation, and aging, (2) age and sex related differences in bone remodeling rates, and (3) limited ability to distinguish between *active* versus *inactive* lesion status at time of death. Lesions which are *active* at time of death provide our best measures of potential age-specific mortality associated with a particular disorder, whereas combined measures of *active* and *healed* lesion frequencies provide us with our best approximation of overall morbidity for the disorder in earlier human groups. However, differential age and sex related bone-specific remodeling rates will distort indices of morbidity derived from skeletal lesions. Thus, the magnitude of such distortion, and the ways in which paleoepidemiologists deal with such phenomena, must be addressed for each particular skeletal lesion that is used to assay disease response in earlier human groups.

Hypothetical Model of Iron Deficiency-Related Porotic Hyperostosis

If it is assumed that iron deficiency anemia was the primary factor involved in the etiology of porotic hyperostosis in a prehistoric human group, a hypothetical model of the expected age and sex specific frequency distributions for unremodeled and remodeled skeletal lesions can be posited. Figure 3a identifies the age and sex specific frequency of occurrence that we would expect to see for porotic hyperostotic lesions that were unremodeled (i.e., active) at time of death. Again, depending upon the sensitivity of the skeletal lesion to the underlying disorder, the overall magnitudes (i.e., frequencies) of the skeletal lesion would be expected to vary from one population to the next due to differential interaction of intrinsic and extrinsic risk factors. Nonetheless, it would be predicted that the ages at onset, peak incidence, and remission would conform to the iron deficiency anemia hypothesis and bracket those

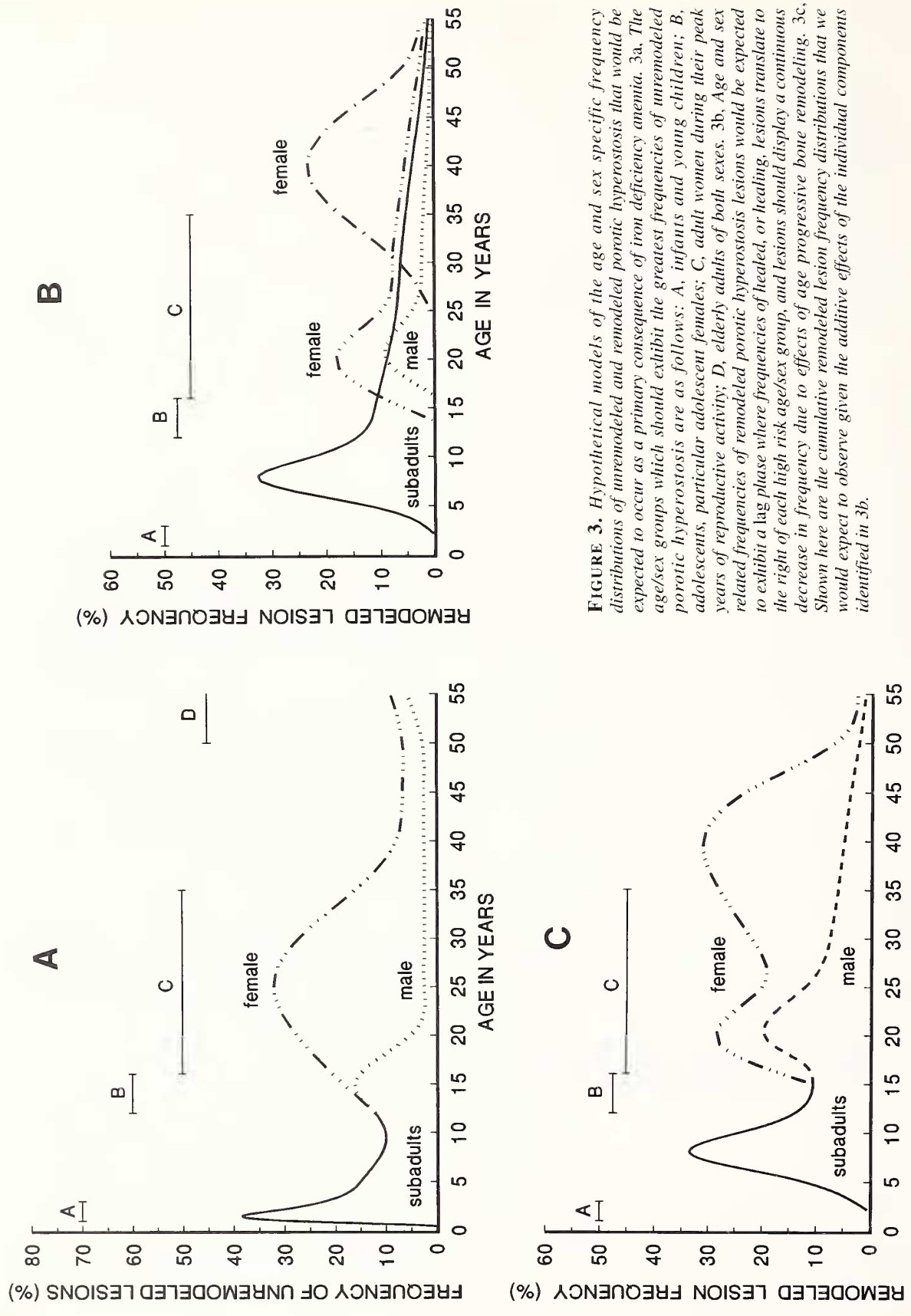

FIGURE 3. *Hypothetical models of the age and sex specific frequency distributions of unremodeled and remodeled porotic hyperostosis that would be expected to occur as a primary consequence of iron deficiency anemia. 3a, The age/sex groups which should exhibit the greatest frequencies of unremodeled porotic hyperostosis are as follows: A, infants and young children; B, adolescents, particular adolescent females; C, adult women during their peak years of reproductive activity; D, elderly adults of both sexes. 3b, Age and sex related frequencies of remodeled porotic hyperostosis lesions would be expected to exhibit a* lag *phase where frequencies of healed, or healing, lesions translate to the right of each high risk age/sex group, and lesions should display a continuous decrease in frequency due to effects of age progressive bone remodeling. 3c, Shown here are the cumulative remodeled lesion frequency distributions that we would expect to observe given the additive effects of the individual components identified in 3b.*

age/sex groups at greatest risk of acquiring the nutritional disorder in each group. These are: A, infants and children that are six months to three years of age; B, adolescents; C, adult females during their peak child-bearing years; and D, post-reproductive adult males and females.

Remodeled lesion frequency distributions shown in Figure 3b should differ from unremodeled lesions in two fundamental ways. First, the ages at onset, peak incidence, and remission for remodeled lesions should display a lag phase and translate to the right of each high risk component in the age distribution. Second, remodeled lesion frequencies should display continuous decay as a result of age progressive bone remodeling.

The cumulative age and sex specific frequency distributions for remodeled porotic hyperostosis that we would expect to observe in a prehistoric skeletal series are shown in Figure 3c. This is an additive representation of information summarized in Figure 3b. Here, it is recognized that several factors will confound our ability to identify remodeled porotic hyperostotic lesions that occurred in association with each high risk age/sex group. The most important among these concerns neurocranial bone remodeling rates. As was discussed earlier, porotic hyperostosis is almost exclusively confined to bony elements of the neurocranium. Growth studies have shown that the human neurocranium achieves 95 percent of adult size by approximately seven years of age (Malina, 1975). Thereafter, neurocranial bone remodeling rates diminish considerably to reach a low level throughout life.

It is thus reasonable to assume that (a) many lesions of slight expression that occurred in the early years of life will be completely remodeled away by adulthood, and (b) a substantial proportion of remodeled lesions that are seen in adults will represent stress episodes that occurred in late infancy, childhood, adolescence, or any combination of these. This results in a circumstance where remodeled lesions will accumulate in young adults, even though these lesions are continuously undergoing reduction in frequency due to a slow rate of age progressive bone remodeling. The remodeled lesion frequency distributions illustrated in Figure 3c therefore represent a more realistic expectation of the cumulative remodeled lesion distributions that would be observed for porotic hyperostosis in earlier human skeletal groups.

With regard to the demographic focus of the hypothetical porotic hyperostosis model, the two most important age/sex groups of interest to the paleoepidemiologist are infants and young children and adult females in their child-bearing years. Elevated levels of subadult mortality that occur as a result of disease and nutritional stress will directly influence both the (a) number of individuals that survive to adulthood, and (b) mean fertility rate that adults must achieve in order to replace the population in succeeding generations. In addition, the latter requirement influences the degree to which nutritional stress may affect the reproductive performance of adult females. It is thus reasonable to presume that such additional compromises may further elevate the mean fertility requirements of the group.

Background for the Libben and Bt-5 Skeletal Populations

Libben is a multi-component Late Woodland cemetery site located in the Black Swamp on the banks of the Portage River in Ottawa County, Ohio. The site was excavated in 1967-1968 and yielded the human skeletal remains of 1,327 individuals that ranged in age from 4 months *in utero* to 50+ years (Lovejoy *et al.*, 1977).[1] Radiocarbon dates ranging from A.D. 850 to A.D. 1250 indicate that the Libben site was formed over a 400 year period, with primary use of the cemetery concentrated in a 200 year span from A.D. 900 to A.D. 1100. Based on ceramic and lithic analyses the Libben site has been assigned to the Younge phase of the Western Basin Tradition.

In contrast to earlier reports (Prufer and Shane, 1976; Lovejoy *et al.*, 1977), no evidence presently exists to support the conclusion that Libben was a semi-permanent village occupied on a year-round basis. It is now clear that the site represents one of a small number of pan-regional cemeteries that was inhabited seasonally, and discontinuously, for several generations (D. Brose, personal communication). The aboriginal peoples that created the Libben site most likely consisted of a small number of culturally affiliated bands which inhabited the northwestern and southwestern shores of Lake Erie, and that placed heavy reliance on local dietary resources (Keenlyside, 1978; Lennox, 1982; Krakker, 1983, 1984; Ferris and Mayer, 1990). These included an abundance of freshwater fish, small mammals, migratory birds, acorn and hickory nuts, several species of berries (Harrison, 1978). In addition, a small quantity of maize was recovered from the site indicating that these peoples also indulged in rudimentary maize horticulture, a finding concordant with observations reported for several other Western Basin Younge phase population groups (see Bowen, 1990; and references therein). Nonetheless, it is quite clear maize horticulture was not an important element in the subsistence economy of the Libben people at this time. Given the number of burials recovered (n=1327), the annual crude death rate observed (CDR=.050), and a two hundred year period of primary use, it is estimated that the Libben cemetery was produced by a small regional population of approximately 130 to 150 individuals distributed among several seasonally mobile bands.

The Carlston Annis Bt-5 shell midden is a sister site of Indian Knoll. It represents a Late Archaic habitation and cemetery site situated on the banks of the Green River in

TABLE 2. *Comparison of Libben and Bt-5 Age-Specific Mortality Rates*

Age Group	Libben			Bt-5			Libben:Bt-5
	d_x	l'_x	q_x	d_x	l'_x	q_x	q_x ratio
0	226	1289	.175	76	354	.215	0.81
1	102	1063	.096	19	278	.068	1.41
3	68	961	.071	10	259	.039	1.82
5	117	893	.131	17	249	.068	1.93
10	94	776	.121	14	232	.060	2.02
15	92	682	.135	27	218	.110	1.23
20	63	590	.107	35	191	.183	0.58
25	78	527	.148	34	156	.218	0.68
30	115	449	.256	31	122	.254	1.01
35	154	334	.461	22	91	.242	1.90
40	97	180	.539	20	69	.290	1.86
45	50	83	.602	18	49	.367	1.64
+50	33	33	1.000	31	31	1.000	1.00
Total	1,289			354			

Symbols: d_x, the absolute number of individuals dead at age$_x$; l'_x, the absolute number of survivors to age$_x$; and q_x, the probability of dying in the succeeding age class for those individuals that survive to age$_x$.

the Western Coalfield region of Kentucky (Webb, 1950). The site was excavated in the late 1930s and early 1940s and yielded the human skeletal remains of approximately 390 individuals ranging in age from 7 months *in utero* to 70+ years (Webb, 1950; Mensforth, 1990).[2] Radiocarbon dates ranging from B.C. 5350 to 2515 indicate that the site was formed over a 2500 year period (Winters, 1974). However, recent studies have shown that the site was occupied most intensively over a 1500 year period from approximately 3500 to 4000 y.b.p. (Marquardt and Watson, 1983). Floral and faunal analyses indicate that Bt-5 was a late summer and fall occupation characteristic of a seasonally mobile semisedentary group. The Bt-5 hunter-gatherers likewise placed heavy reliance on local dietary resources. These included mussels, deer, turkey, waterfowl, and an abundance of hickory nuts and acorns (Marquardt, 1972; Winters, 1974; Marquardt and Watson, 1983). Although seven small fragments of squash were recovered at Bt-5, it is very unlikely that this domesticated cultigen contributed to the subsistence economy of these peoples. Alternatively, it has been suggested that people of the Late Archaic Green River Culture may have made occasional use of squash gourds as containers, thus implying a utilitarian function (Marquardt and Watson, 1983). Given estimates of regional site density, length of occupation, and ethnographic analogy, it has been suggested that individual groups ranged in size from 30 to 50 individuals per given time (May, 1969).

Paleodemographic reconstructions and composite life table analyses with archetype fertility data are currently available for Libben and Bt-5 (Lovejoy *et al.*, 1977; Mensforth, 1990). Age-specific mortality rates for the two skeletal populations and mortality ratios which compare the two groups are given in Table 2. It can be seen that infants and children are well represented in each group. Thus, census error due to infant underenumeration is not problematic.

The similarities which characterize the Libben and Bt-5 demographic profiles are as follows. Both skeletal groups exhibit (1) type II survivorship curves, (2) high infant mortality, (3) low mortality in the adolescent years, (3) early onset of elevated mortality rates in young adults, and (4) a sex differential in adult survivorship where males over 35 years of age experience higher death rates relative to females. However, the latter trends that were observed in each group are statistically insignificant (Lovejoy *et al.*, 1977; Mensforth, 1990).

The manner in which Libben and Bt-5 demographic parameters differ are as follows. Ratios that compare Libben and Bt-5 age-specific mortality rates are given in Table 2. Except for infants in the first year of life and 3rd decade adults, it can be seen that Libben mortality rates exceed those of Bt-5 at all ages. A comparison of

survivorship at age 15 (l_{15}: Libben, 52.9; Bt-5, 61.6) shows that 8.7 percent fewer Libben individuals survived to adulthood relative to Bt-5. This difference in subadult survivorship is statistically significant (χ^2=8.43, p<.01). A comparison of Libben and Bt-5 dependency ratios (Libben, .89; Bt-5, .69) calculated according to Howell (1982) yields a figure for the Libben group that is 29 percent greater relative to Bt-5. Furthermore, a comparison of average age-specific rates ($\bar{B}$: Libben, .083; Bt-5, .076) shows that Libben adult females must have maintained a $\bar{B}$ that was 9.2 percent higher than Bt-5 in order to replace the population in succeeding generations. The mean age-specific fertility rates reported here were calculated using archetypal fertility data assembled by Weiss (1973). With regard to adult age distributions, Kolmogorov-Smirnov two sample tests indicate that no significant differences characterize the two groups. These findings apply to inter-group comparisons of total adults and adults partitioned by sex.

Information described above shows that the Libben and Bt-5 groups differed primarily with respect to levels of subadult mortality. The mortality data listed in Table 2 indicates that the first year death rate at Bt-5 was 19 percent greater than Libben. However, for all other subadult age classes, Libben mortality rates exceed those of Bt-5 by 40-102 percent. These findings are of interest for the following reason. Gordon and associates (1967) have shown that first year death rates vary considerably in modern underdeveloped societies, whereas patterns of childhood mortality, second year death rates in particular, provide a superior index of the nutritional health status of a population. On the basis of demographic inference, it is reasonable to hypothesize that Libben subadults experienced greater levels of disease and nutritional stress that resulted in elevated subadult mortality relative to the Bt-5 group. As a corollary, it would be predicted that patterns in the frequency of occurrence of porotic hyperostosis would corroborate this circumstance. Thus, the paleoepidemiology of porotic hyperostosis in the Libben and Bt-5 skeletal populations was examined in the manner outlined below.

Materials and Methods

The cranial remains of all Libben and Bt-5 skeletons were macroscopically examined for the presence/absence of porotic hyperostosis. Only those specimens that provided combined observations for the superior orbital plates, frontal, parietal, and occipital bones were included in epidemiological analyses. This yielded a combined sample of 827 individuals (Libben, *n*=580; Bt-5, *n*=247) that ranged in age from birth to 50+ years.

Patterns of skeletal involvement and lesion activity status that characterized porotic hyperostosis were assessed in the following manner. All lesions were initially classified as orbital or extra-orbital.[3] Orbital lesions refer to those that were confined to the superior orbital plates (i.e., cribra orbitalia), whereas extra-orbital lesions refer to those which were noted to affect the pericranial surfaces of the frontal, parietal, or occipital bones.[4] Lesions were then qualitatively evaluated as displaying slight, moderate, or extensive osseous tissue response to the stimulus of bone marrow proliferation. Finally, all lesions were classified as remodeled or unremodeled based on qualitative assessment of bone texture and formative versus resorptive bone activity. The criteria which were used to distinguish between remodeled and unremodeled lesions were as follows:

a) Unremodeled Porotic Hyperostosis

During the initial phase of manifestation, lesions of minimal expression appear as small localized concentrations of microporosity that are situated on the surface of an affected bone. As the pathological skeletal response becomes more pronounced, hypertrophy of osseous tissue becomes apparent and the lesion usually acquires a well-defined microporous cribriform mesh. At this stage the pore channels enlarge, coalesce, and give rise to macropores which often show irregular or trabeculated margins. In general, unremodeled lesions characteristically exhibit sharp, well-defined pore margins. Microporosity, both within and peripheral to the cribriform mesh, is typically present and visible upon close macroscopic examination. Pore channels project outward from the diploic space and are characteristically oriented perpendicular to the surface of an affected bone. The active lesion typically displays a fibrous texture that is characteristic of immature woven bone. If present, superficial hypervascular channels tend to be well-developed and may occur within, or peripheral to, the lesion proper. (See Figures 4a-c.)

b) Remodeled Porotic Hyperostosis

Inactive lesions typically exhibit progressive bone filling of the central and peripheral pores. The extent to which bone replacement occurs is highly variable. Pore margins are usually smooth and rounded, and microporosity in the cribriform mesh undergoes substantial reduction. The lesion displays a smooth texture that is characteristic of mature lamellar bone. Also, pore channels often become increasingly oblique in orientation relative to the surface of an affected bone. Although microporosity that is characteristic of an unremodeled lesion is usually absent, remodeled lesions often display a secondary microporosity which is the consequence of bone-filling of the pores. This results in a substantial reduction in diameter of individual pores. In addition, superficial

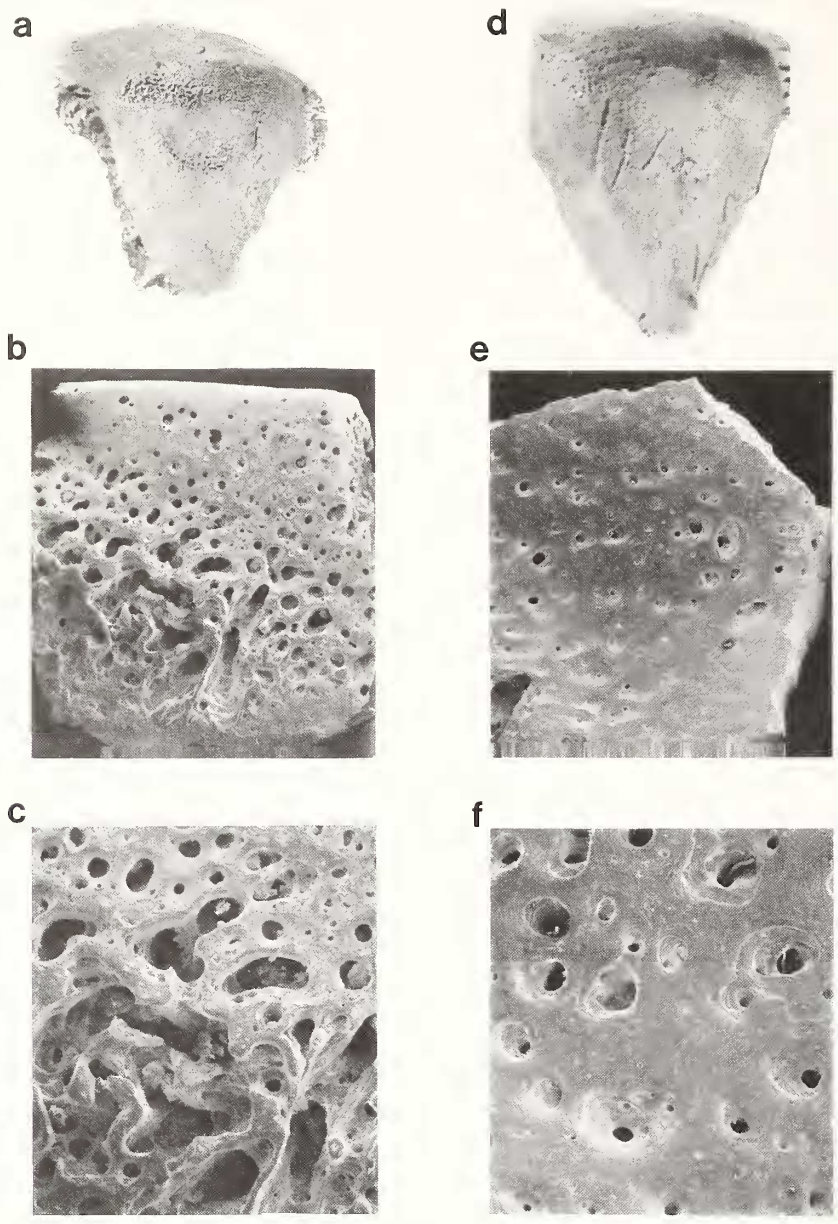

FIGURE 4. *Photographs, and scanning electron microscope images, of unremodeled and remodeled porotic hyperostosis lesions.* 4a, *Inferior view of the left superior orbital plate of a Libben child (KSU-01252, 2-3 years) with multiple porotic hyperostotic lesions at time of death. The lesion situated along the anterior margin of the superior orbital plate is unremodeled. It displays a well-developed cribriform mesh, woven bone texture, microporosity, and well defined pore margins. The SEM images of this specimen magnified 8x* (4b) *and 16x* (4c) *illustrate these characteristics more clearly. The remodeled lesion in the central portion of the superior orbital plate exhibits a lamellar textured cribriform mesh, loss of microporosity due to bone-filling of pore channels via appositional bone remodeling, irregular orientation of pore channels, and residual hypervascularity.* 4d, *Inferior view of the left superior orbital plate of a Libben child (KSU-00222a, 5-6 years) that displayed a remodeled porotic hyperostotic lesion at time of death. The qualitative features of this specimen are likewise illustrated in SEM images magnified 8x* (4e) *and 16x* (4f). *Note the loss of microporosity in the cribriform mesh, the acquisition of a lamellar bone texture, reduction of pore diameter due to subsequent bone-filling, and retention of residual hypervascular channels. In some circumstances, lesion remodeling may be so extensive as to completely obliterate pores and give rise to the appearance of a* dimpled *surface topography on an affected bone.*

hypervascular channels of variable definition may be retained as a residual artifact of the initial pathological response. (See Figures 4d-f.)

In the present study, remodeled lesions are regarded as a pathological skeletal change that occurred in response to an earlier stress episode which was inactive, or in the process of remission, at time of death. Unremodeled lesions are regarded as indicating that erythroid marrow hyperplasia was active at the time of death of an affected individual, and thus served as the basis for establishing the age-specific frequency of occurrence for porotic hyperostosis that was observed in the two skeletal series.

The age classification which was used to evaluate Libben and Bt-5 subadult porotic hyperostosis was selected on the basis of well-documented age-specific risk factors that relate disease and nutritional stress to patterns of infant and child morbidity and mortality (Gordon *et al.*, 1963). These age intervals are defined as follows: birth to 6 months, six to twelve months, one to three years, and three to five years. Five year age intervals were used to evaluate the frequency of porotic hyperostosis in all individuals that were over five years of age at time of death.

Libben and Bt-5 subadults (0-15 years) were aged on the basis of (1) dental maturation in accordance with published standards for crown and root development, and (2) polynomial regressions that correlated population-specific standards for long bone diaphyseal lengths attained with dental maturation (Lovejoy *et al.*, 1977; Mensforth, 1990). Age determinations for Libben and Bt-5 adults (+15 years) were accomplished by the multifactorial summary age method (Lovejoy *et al.*, 1985). This procedure employed (1) multiple indicators of skeletal age at death (Libben, n=6; Bt-5, n=5), (2) independent age indicator seriation, and (3) differential weighting of summary age estimates as determined by principal components analysis (Lovejoy *et al.*, 1977; Mensforth, 1990). Adult sex diagnoses for the two skeletal series were based on standard pelvic and cranial morphological criteria (Krogman and Iscan, 1986).

Because porotic hyperostosis is a non-specific skeletal response to the stimulus of erythroid marrow hyperplasia, differential diagnoses were required to evaluate the roles that iron deficiency anemia and/or hemolytic anemias may have played in the pathogenesis of the lesion in the Libben and Bt-5 skeletal populations. Therefore, all cranial and post-cranial materials were carefully surveyed for the presence/absence of skeletal changes that are considered pathognomonic for those conditions which are regarded as major factors in the etiology of porotic hyperostosis in earlier human groups (Moseley, 1974).

Results of the analyses have been summarized in graphic and tabular form. Appropriate nonparametric statistics were used to evaluate the demographic composition and fidelity of the skeletal pathology samples, and intra-and-interpopulational patterns in the frequency of occurrence of porotic hyperostosis that were observed in the Libben and Bt-5 skeletal populations.

Results

Demographic Composition of the Libben and Bt-5 Skeletal Samples

The extent to which samples available for the study of one or more skeletal disorders adequately reflect the demographic characteristics of the populations from which they were derived is a question that paleoepidemiologists have rarely addressed. It is well recognized that (a) cultural biases at time of deposition, (b) taphonomic factors involved in processes of site formation and decay, and (c) selective recovery practices can all strongly influence differential preservation of skeletal remains. The degree to which the latter occurs can markedly restrict the availability and utility of skeletal samples that are of interest for scientific reasons.

For the Libben and Bt-5 skeletal groups, both (a) subadults and adults, and (b) cranial and post-cranial remains are well represented. In addition, the age/sex distribution of individuals within each cemetery was random. Thus, cultural biases at time of deposition and selective recovery practices are not problematic for these two groups. However, a comparison of differential preservation shows that only 45 percent (580/1289) of the total number of individuals identified and recovered from the Libben site presented intact or fragmentary cranial remains that were sufficiently preserved that could be scored for the presence/absence of porotic hyperostosis. For Bt-5, 69.8 percent (247/354) of individuals recovered from the site could be examined for bony evidence of erythroid marrow hyperplasia.

Therefore, age distributions for the Libben and Bt-5 reduced samples of specimens that could be examined for the presence/absence of porotic hyperostosis were compared to the age distributions for the larger demographic samples that characterize each skeletal sample. These data are summarized in Table 3. Kolmogorov-Smirnov values show that all comparisons were insignificant. It is concluded that the demographic composition of the skeletal samples used to investigate porotic hyperostosis in this study provide an accurate representation of the populations from which they are derived.

General Observations

All individuals with porotic hyperostosis that were identified in the initial survey were re-examined on a second occasion. This procedure ensured that bony changes due to normal patterns of bone growth and remodeling, and other pathological conditions, would not be mistakenly diagnosed as porotic hyperostosis. Skeletal changes that in some ways resembled porotic hyperostosis were seen most often in infants and in adults over 45 years

TABLE 3. *Kolmogorov-Smirnov Values for Tests Comparing Age Distributions for the Libben and Bt-5 Demographic Study Samples and the Samples That Were Available for the Study of Porotic Hyperostosis Frequencies in Each Group*

		Demographic Sample	Porotic Hyperostosis Sample		
Skeletal Series	*Age/Sex Group*	n_1	n_2	$D_{max.}$	$D_{crit.}$
Bt-5	Subadults	136	100	.018	.179
	Adult Males	108	71	.021	.208
	Adult Females	110	76	.054	.203
Libben*	Subadults	607	310	.035	.095
	Adult Males	184*	137	.079	.153
	Adult Females	171*	133	.076	.157

* The Libben adult male and female demographic sample *n*'s consist of only those adults for which sex has been estimated and listed in the Libben site skeletal records (see Lovejoy et al., 1977). The values for $D_{crit.}$ that are reported above represent the critical values for two-tailed K-S tests at the .05 level of probability.

of age. Infants, particularly those under six months of age, often displayed regular patterns of woven bone deposition associated with variable degrees of microporosity. These skeletal changes are best regarded as normal patterns of cranial appositional bone growth at this age. Although uncommon, infants and children from 3 to 18 months of age were also prone to exhibit periosteal reaetions affecting the endocranial surfaces of cranial vault bones and the superior orbital plates. These lesions appear as a scab over the normal surface of an affected bone, exhibit variable microporosity, and occur as a consequence of subperiosteal hemorrhage due to venous sinus thrombosis (Mensforth *et al.*, 1978).

In contrast, older adults often displayed variable degrees of osteoporotic pitting of the cranial vault bones that in some ways mimic remodeled porotic hyperostosis. However, these skeletal changes are primarily restricted to the outer surfaces of affected bones, do not involve the marrow space, and are best regarded as an age-related consequence of bone involution. Therefore, all Libben and Bt-5 individuals that displayed porotic hyperostosis *mimics* were excluded from further consideration.

Total Frequency of Occurrence and Degree of Involvement for Libben and Bt-5 Porotic Hyperostosis

The total frequency with which porotic hyperostosis was observed in the Libben and Bt-5 skeletal series is summarized in Table 4. Thus, 35 percent of Libben and 20.6 percent of Bt-5 individuals displayed either remodeled or unremodeled lesions at time of death. Libben and Bt-5 individuals showed a frequency of unremodeled lesions that approximated 20 percent and 10 percent, respectively. Chi square comparisons indicate that the Libben group experienced a significantly greater frequency of unremodeled and total lesions relative to the Bt-5 group (unremodeled lesions χ^2=11.95, p<.001; remodeled lesions χ^2=2.94, p>.05; total lesions χ^2=16.77, p<.001).

With regard to degree of involvement, it was found that the majority of Libben and Bt-5 porotic hyperostotic lesions were the result of a minimal osseous tissue response to the stimulus of erythroid marrow hyperplasia. Among subadults, lesions of slight expression occurred in 85.1 percent (114/134) of Libben and 87.0 percent (20/23) of Bt-5 individuals. Lesions of moderate expression were observed in only 14.2 percent (19/134) of Libben and 13.0 percent (3/23) of Bt-5 subadults. The majority of moderate tissue responses occurred in specimens that ranged in age from six months to three years of age at time of death in each skeletal series. Only one Libben child displayed severe porotic hyperostosis (see Figure 1a). No Bt-5 subadults were affected to such a degree.

No adults in either skeletal series displayed severe bony changes in response to erythroid marrow hyperplasia. Lesions of slight and moderate expression occurred in 95.7 percent (66/69) and 4.3 percent (3/69) of Libben adults with porotic hyperostosis, respectively. All lesions that were encountered in Bt-5 adults were slight involvements. In addition, all lesions that were identified in Libben and Bt-5 adults were confined to the superior orbital plates.

TABLE 4. *Comparison of the Total Frequency With Which Porotic Hyperostosis Was Observed in the Libben and Bt-5 Skeletal Groups*

		Unremodeled Lesions		Remodeled Lesions		Total Lesions	
Skeletal Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)
Bt-5	247	25	10.1	26	10.5	51	20.6
Libben*	580	116	20.0	87	15.0	203	35.0
Total	827	141	17.0	113	13.7	254	30.7

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis; n_2, number of specimens that were scored positive for unremodeled lesions; n_3, number of specimens that were scored positive for remodeled lesions; n_4, total number of specimens that were scored positive for remodeled or unremodeled lesions.

* Chi square values indicate that the Libben group experienced a statistically significantly greater frequency greater frequency of unremodeled and total porotic hyperostotic lesions compared to the Bt-5 group (unremodeled lesions, χ^2=11.95; remodeled lesions, χ^2=2.94;total lesions, χ^2=16.77).

Age and Sex Specific Frequency Distributions for Unremodeled Porotic Hyperostosis

Data enumerating the age and sex specific frequency of occurrence for porotic hyperostosis in the Libben and Bt-5 skeletal groups are given in Tables 5, 6, 7, and 8. Chi square values that compare the total frequency with which remodeled and unremodeled lesions were observed in subadults and adults partitioned by sex in the two skeletal series are listed in Tables 9 and 10, respectively.

The general similarities that were observed for each groups are as follows: (1) subadults displayed the highest frequency of unremodeled and total lesions at time of death, (2) adult females showed the second highest frequency of unremodeled and total lesions, and (3) adult males exhibited the lowest frequency of unremodeled and total lesions. The only exception to the pattern described above was that Bt-5 adult females displayed a slightly greater frequency of total lesions than subadults in this group.

The Libben rank order frequency for total lesions observed is subadults (43.2%), adult females (35.3%), and adult males (16.1%). The comparable information for Bt-5 is adult females (25.0%), subadults (23.0%), and adult males (12.7%). The Libben rank order frequency for lesions that were unremodeled at time of death is subadults (30.3%), adult females (14.3%), and adult males (2.2%). The comparable Bt-5 rank order is subadults (14%), adult females (8.8%), and adult males (2.8%).

Chi square values for within group comparisons (see

TABLE 5. *Age-Specific Frequency of Occurrence for Porotic Hyperostosis in Libben Subadults (0-15 years)*

		Unremodeled Lesions		Remodeled Lesions		Total Lesions		Extra-orbital Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_5	(%)
0.0 - 0.5	61	0	0.0	0	0.0	0	0.0	0	0.0
0.5 - 1.0	38	10	26.3	0	0.0	10	26.3	7	18.4
1.0 - 3.0	71	45	63.4	6	8.4	51	71.8	18	25.4
3.0 - 5.0	26	8	30.8	7	26.9	15	57.7	2	7.7
5.0 -10.0	54	14	25.9	17	31.5	31	57.4	4	7.4
10.0 -15.0	60	17	28.3	10	16.7	27	45.0	2	3.3
Total	310	94	30.3	40	12.9	134	43.2	33	10.7

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, number of specimens that exhibited remodeled and/or unremodeled lesions per age group; n_5, number of specimens that manifested extra-orbital lesions per age group.

TABLE 6. *Age-Specific Frequency of Occurrence for Porotic Hyperostosis in Libben Adults*

	Female							*Male*						
		Unremodeled Lesions		Remodeled Lesions		Total Lesions			Unremodeled Lesions		Remodeled Lesions		Total Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_1	n_2	(%)	n_3	(%)	n_4	(%)
15 - 19	18	6	33.3	5	27.8	11	61.1	16	1	6.3	4	25.0	5	31.3
20 - 24	17	5	29.4	3	17.7	8	47.1	17	0	0.0	3	17.7	3	17.7
25 - 29	17	1	5.9	4	23.5	5	29.4	17	1	5.9	4	23.5	5	29.4
30 - 34	15	1	6.7	3	20.0	4	26.7	31	0	0.0	4	12.9	4	12.9
35 - 39	17	1	5.9	4	23.5	5	29.4	30	1	3.3	2	6.7	3	10.0
40 - 44	26	2	7.7	8	30.8	10	38.5	11	0	0.0	1	1.9	1	1.9
45 - 49	13	2	15.4	1	7.7	3	23.1	9	0	0.0	1	11.1	1	11.1
+50	10	1	10.0	0	0.0	1	10.0	6	0	0.0	0	0.0	0	0.0
Total	133	19	14.3	28	21.0	47	35.3	137	3	2.2	19	13.9	22	16.1

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, total number of specimens that were scored positive for remodeled or unremodeled lesions per age group.

TABLE 7. *Age-Specific Frequency of Occurrence for Porotic Hyperostosis in Bt-5 Subadults (0-15 years)*

		Unremodeled Lesions		Remodeled Lesions		Total Lesions		Extra-orbital Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_5	(%)
0.0 - 0.5	38	0	0.0	0	0.0	0	0.0	0	0.0
0.5 - 1.0	17	3	17.7	0	0.0	3	17.7	2	12.5
1.0 - 3.0	14	7	50.0	1	7.1	8	57.1	0	0.0
3.0 - 5.0	10	1	10.0	3	30.0	4	40.0	0	0.0
5.0 -10.0	9	1	11.1	3	33.3	4	44.4	1	11.1
10.0 -15.0	12	2	16.7	2	16.7	4	33.4	0	0.0
Total	100	14	14.0	9	9.0	23	3.0	3	3.0

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, number of specimens that exhibited remodeled and/or unremodeled lesions per age group; n_5, number of specimens that manifested extra-orbital lesions per age group.

TABLE 8. *Age-Specific Frequency of Occurrence for Porotic Hyperostosis in Bt-5 Adults*

	Female							*Male*						
		Unremodeled Lesions		Remodeled Lesions		Total Lesions			Unremodeled Lesions		Remodeled Lesions		Total Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_1	n_2	(%)	n_3	(%)	n_4	(%)
15 - 19	9	1	11.1	3	33.3	4	44.4	10	0	0.0	0	0.0	0	0.0
20 - 24	8	2	25.0	1	12.5	3	37.5	13	1	7.7	1	7.7	2	15.4
25 - 29	10	2	20.0	1	10.0	3	30.0	12	0	0.0	1	8.3	1	8.3
30 - 34	9	0	0.0	1	11.1	1	11.1	11	0	0.0	3	27.3	3	27.3
35 - 39	7	1	14.3	1	14.3	2	28.6	7	0	0.0	1	14.3	1	14.3
40 - 44	7	0	0.0	0	0.0	0	0.0	8	0	0.0	0	0.0	0	0.0
45 - 49	8	1	12.5	0	0.0	1	12.5	5	1	20.0	0	0.0	1	20.0
+50	18	2	11.1	3	16.7	5	27.8	5	0	0.0	1	20.0	1	20.0
Total	76	9	11.8	10	13.2	19	25.0	71	2	2.8	7	9.9	9	12.7

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, total number of specimens that were scored positive for remodeled or unremodeled lesions per age group.

TABLE 9. *Chi Square Values for Within-Group Comparisons of the Frequency of Occurrence for Porotic Hyperostosis in the Libben and Bt-5 Skeletal Samples*

	Libben		Bt-5	
Age and Sex Group Comparisons	*Unremodeled Lesions*	*Total Lesions*	*Unremodeled Lesions*	*Total Lesions*
Subadults vs. Adults	44.35[a]	19.81[a]	2.78	0.57
Subadults vs. Adult Males	44.26[a]	30.87[a]	6.12[b]	4.56[b]
Subadults vs. Adult Females	12.60[a]	2.40	0.18	0.10
Adult Males vs. Adult Females	13.19[a]	13.19[a]	4.32[b]	3.62

a: significant at the .001 level of probability.
b: significant at the .05 level of probability.

Table 9) show that subadults in each group experienced a significantly greater frequency of unremodeled and total lesions compared to adult males, and adult females displayed a significantly greater frequency of unremodeled lesions compared to adult males. In addition, Libben subadults had a significantly greater incidence of unremodeled lesions compared to adult females. Therefore, both skeletal groups are characterized by marked age and sex differences in the frequency of occurrence of porotic hyperostosis. The only exception to this was that Bt-5 subadults and adult females showed no significant differences in the frequency of unremodeled or total lesions that were observed. Chi square values for between group comparisons (see Table 10) show that the only significant difference between Libben and Bt-5 was confined to subadults. Here, Libben subadults displayed a significantly greater frequency of unremodeled and total lesions compared to Bt-5 subadults.

The age and sex specific frequencies with which unremodeled porotic hyperostosis occurred in the Libben and Bt-5 groups are illustrated in Figures 5a and 5b. These frequency distributions identify those age/sex groups where erythroid marrow hyperplasia was sufficiently active to invoke a skeletal response at, or near, time of death. It was previously shown that Libben and Bt-5 adults are characterized by a low incidence of unremodeled porotic hyperostosis. Therefore, unremodeled lesion frequency data for adults over 20 years of age are plotted by decade here in order to smooth effects of small subsample sizes combined with low overall incidence.

Comparisons of Libben and Bt-5 age-related porotic hyperostosis frequency distributions for subadults are illustrated more clearly in Figure 6. These patterns show that the lesion bears a strong relationship with developmental age. The following general relationships characterize subadults in both skeletal series. No lesions were seen in individuals that were under six months of age at time of death. A low incidence of unremodeled porotic hyperostosis first occurred in the six to twelve month period. During the one to three year period the frequency of unremodeled lesions increased dramatically to reach peak incidence in each group. Subsequently, the frequency of active lesions decreased throughout the childhood years. During the adolescent period the frequency of unremodeled porotic hyperostosis showed a slight increase once again.

Figures 6a-c show that the age at onset, peak incidence, and age at remission for unremodeled porotic hyperostosis are virtually identical in Libben and Bt-5 subadults. Chi square values listed in Table 11 indicate that Libben subadult age-related patterns for unremodeled porotic hyperostosis are statistically significant. The absence of lesions prior to six months of age, peak incidence in the one to three year period, and subsequent decline are all well defined. Chi square values for the Bt-5 subadults show a similar, though less pronounced, trend. This is primarily

TABLE 10. *Chi Square Values for Between-Group Comparisons of the Frequency of Occurrence for Porotic Hyperostosis in the Libben and Bt-5 Skeletal Samples*

	Chi Square Values	
Age Group	*Unremodeled Lesions*	*Total Lesions*
Subadults	10.38[b]	13.09[a]
Adult Females	0.25	2.39
Adult Males	0.08	0.51
Total Adults	0.06	2.26

a: significant at the .001 level of probability.
b: significant at the .01 level of probability.

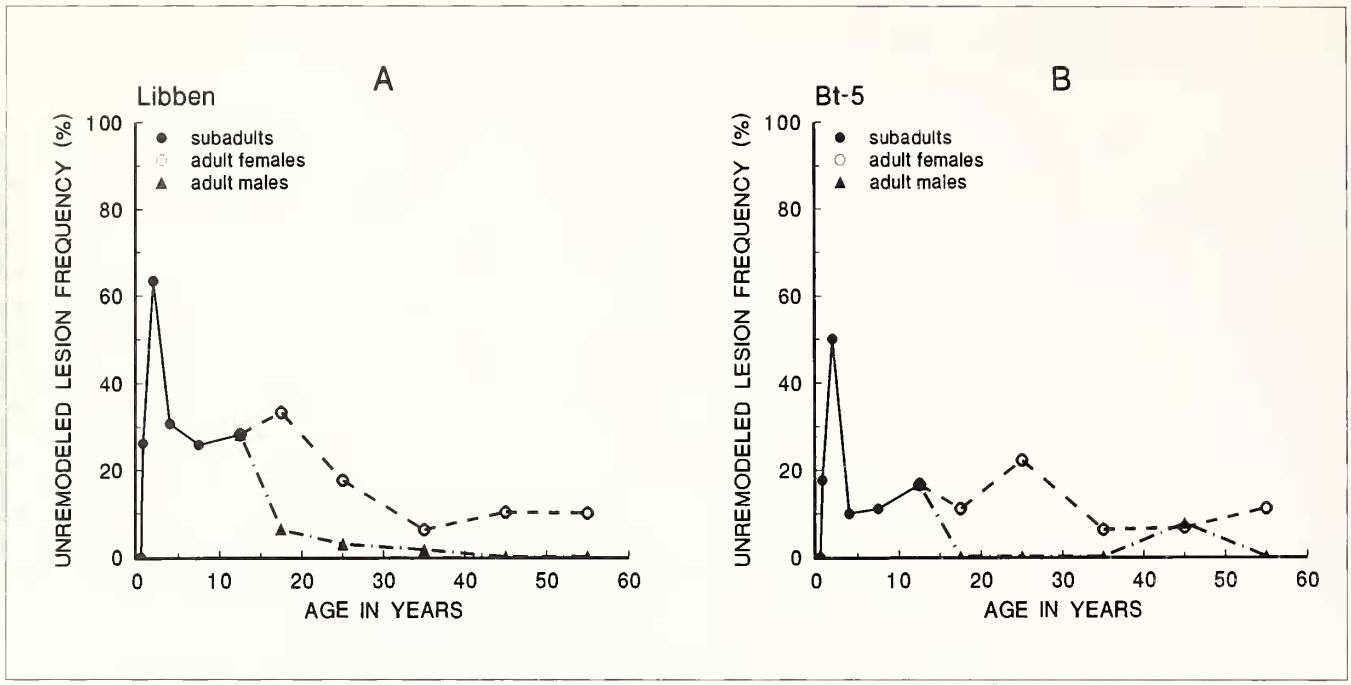

FIGURE 5. *Age and sex specific frequencies of occurrence for unremodeled porotic hyperostosis that were observed in the Libben* (5a) *and Bt-5* (5b) *skeletal samples. Individuals over 15 years of age are partitioned by sex.*

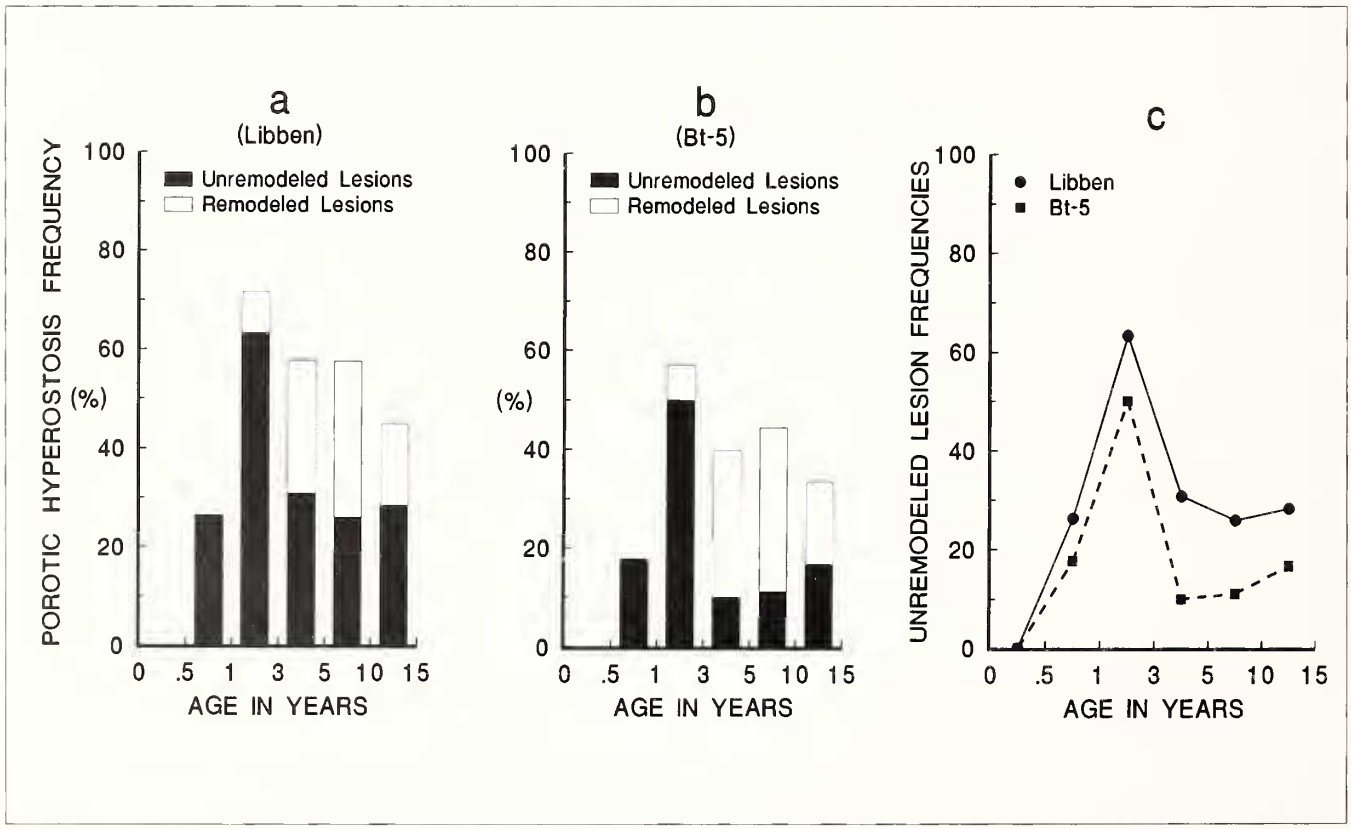

FIGURE 6. *Histograms and polygon frequencies that compare the age-specific frequencies of occurrence for unremodeled* (6a-c) *and remodeled* (6a-b) *porotic hyperostosis in Libben and Bt-5 subadults ranging in age from birth to 15 years at time of death.*

TABLE 11. *Chi Square Values for Within-Group Comparisons of the Age-Specific Frequency of Occurrence for Unremodeled Porotic Hyperostosis in Libben and Bt-5 Subadults*

		Age Group			
Age Group	*Skeletal Group*	*1-3*	*3-5*	*5-10*	*10-15*
0.5 - 1.0	Libben	13.60[a]	0.35	0.26	0.05
	Bt-5	3.68	0.29	0.19	0.00
1.0 - 3.0	Libben		6.57[b]	23.57[a]	16.02[a]
	Bt-5		4.20[b]	3.65	3.17
3.0 - 5.0	Libben			1.22	0.21
	Bt-5			0.01	0.21
5.0-10.0	Libben				0.69
	Bt-5				0.13

a: significant at the .001 level of probability.
b: significant at the .05 level of probability.

due to the fact that a smaller number of Bt-5 subadults were available for comparison in each age class.

Further reference to Figures 6a-c shows that Libben subadults consistently displayed a greater frequency of unremodeled and total lesions per age class compared to Bt-5. Chi square values given in Table 12 indicate that none of the subadult age class comparisons between the two groups are statistically significant. However, this is not surprising given that unremodeled lesions in both groups displayed a marked conformity in age specific distribution, and a much smaller number of Bt-5 subadults were available for comparisons.

Among adult females in each group it can be seen that the highest frequency of unremodeled porotic hyperostosis occurred in individuals that were 15 to 30 years of age at time of death. Thereafter, adult females displayed a low frequency of unremodeled lesions. In contrast, adult males in each group showed a low frequency of unremodeled lesions at all ages. Therefore, the patterns that were observed for porotic hyperostosis indicate that (1) the ages at onset, peak incidence, and remission for unremodeled lesions are markedly similar in the two band level societies, and (2) the frequency distributions that characterize unremodeled lesions identify those age/sex groups at highest risk of acquiring iron deficiency anemia.

Age/Sex Frequency Distributions for Remodeled Porotic Hyperostosis

Among those subadults that displayed porotic hyperostosis in the two skeletal series (see Tables 5 and 7), remodeled lesions were observed in 29.9 percent (40/134) of Libben and 39.1 percent (9/23) of Bt-5 individuals. Thus, the majority of subadults with porotic hyperostosis in the two skeletal series had active lesions at time of death. In contrast, the vast majority of adults with porotic hyperostosis had remodeled lesions at time of death. In Libben adults with porotic hyperostosis, remodeled lesions were seen in 86.4 percent (19/22) of affected males and 59.6 percent (28/47) of affected females (see Table 6). Similarly, in Bt-5 adults with porotic hyperostosis, remodeled lesions occurred in 77.8 percent (7/9) of affected males and 52.6 percent (10/19) of affected females (see Table 8).

TABLE 12. *Chi Square Values That Compare the Age-Specific and Total Frequency of Occurrence for Porotic Hyperostosis Among Libben and Bt-5 Subadults*

	Chi Square Values		
Age Group	*Unremodeled Lesions*	*Remodeled Lesions*	*Total Lesions*
0.5 - 1.0	0.49	—	0.49
1.0 - 3.0	0.88	0.03	1.19
3.0 - 5.0	1.66	0.03	0.91
5.0 -10.0	0.93	0.01	0.53
10.0 -15.0	0.70	0.00	0.56
Total	10.38[b]	1.09	13.09[a]

a: significant at the .001 level of probability.
b: significant at the .01 level of probability.

TABLE 13. *Porotic Hyperostosis Frequency Data and Chi Square Values That Compare Adult Females 12-30 Years of Age Versus Those +30 Years of Age*

			Lesion Frequency					
			Unremodeled Lesions		Total Lesions		Chi Square Values	
Adult Female Samples	*Age Group*	n_1	n_2	(%)	n_3	(%)	*Unremodeled Lesions*	*Remodeled Lesions*
Libben	15-30	52	12	23.1	24	46.2	5.39[b]	4.37[b]
	+30	81	7	8.6	23	28.4		
Bt-5	15-30	27	5	18.5	10	37.0	1.79	3.24
	+30	49	4	8.2	9	18.4		
Combined	15-30	79	17	21.5	34	43.0	7.22[a]	7.22[a]
	+30	130	11	8.5	32	24.6		

Symbols: n_1, total number of adult females that could be scored for the presence/absence of porotic hyperostosis per age group; n_2, number of adult females that were scored positive for unremodeled lesions per age group; n_3, total number of individuals that were scored positive for remodeled or unremodeled lesions per age group; *a*, Chi square values significant at the .01 level of probability; *b*, Chi square values significant at the .05 level of probability.

The similarities which characterize the age-specific frequency of remodeled lesions that occurred in the two groups are as follows. A low incidence of remodeled lesions first appeared in the one to three year period. The frequency of remodeled lesions gradually increased to reach peak incidence in the five to ten year period in each group. A low frequency of remodeled lesions was once again seen in adolescents. Remodeled lesions in adults were most commonly seen in individuals that ranged in age from 15 to 35 years in each group. The only exception to this was that Libben females over 35 years of age showed a remodeled lesion frequency which was 14.8 percent higher compared to young adult females. However, the latter difference is statistically insignificant (χ^2=1.04; p>.05).

Age Related Porotic Hyperostosis Frequency Distribution in Adult Females

Archetype fertility data reported by Weiss (1973) show that age specific fertility rates in contemporary primitive societies are highest in adult females that are 15 to 30 years of age. As a corollary, it would be predicted that peak periods of reproductive activity would predispose young women to a greater incidence of iron deficiency anemia. The latter would give rise to variable levels of erythroid marrow hyperplasia and result in a greater frequency of unremodeled porotic hyperostosis in these individuals. Therefore, Libben and Bt-5 adult female age-related porotic hyperostosis frequency distributions were assessed in the following manner.

Information summarized in Table 13 compares the frequencies with which unremodeled porotic hyperostosis, and total lesions, occurred in Libben and Bt-5 adult females that were 15 to 30 years of age versus those that were +30 years of age at time of death. For the 15 to 30 year age group results show that 23.1 percent of Libben females and 18.5 percent of Bt-5 females had unremodeled lesions at time of death. Libben and Bt-5 adult females that were over 30 years of age displayed unremodeled lesion frequencies of 8.6 percent and 8.2 percent, respectively. Thus, young adult females in both groups exhibited a greater frequency of unremodeled lesions compared to their older peers (Libben, 14.5% higher; Bt-5, 10.3% higher). However, chi square values listed in Table 11 indicate that this difference is only signifieant for Libben adult females.

Comparisons of total lesion frequencies that were observed for Libben and Bt-5 adult female age categories yielded similar results. However, these data are inappropriate for the following reason. Remodeled lesions that occurred in association with childhood and adolescent stress episodes are likely to accumulate in young adults where a substantial degree of age-progressive bone remodeling has not yet occurred. In contrast, it would be expected that many *lesions of youth* would be completely remodeled away in older individuals. Therefore (1) age-progressive bone remodeling alone can give rise to age related differences in the frequency of occurrence for porotic hyperostosis in adults, and (2) combined measures of remodeled and unremodeled porotic hyperostosis that disregard lesion activity status at time of death will result in inflated young adult lesion frequencies and deflated older adult lesion frequencies.

Age/Sex Frequency Distribution for the Libben and Bt-5 Porotic Hyperostosis Macrosample: a Test of the Iron Deficiency Anemia Hypothesis

Paleoepidemiological analyses of skeletal pathologies have generally emphasized the comparative approach. Here, the primary goals are to identify and interpret the ways in which two or more skeletal series differ. Nonetheless, the only way to evaluate the extent to which one or more factors may have played a common role in the etiology of a stress indicator is to examine the similarities in lesion frequency patterns that characterize two or more skeletal groups. This can be accomplished, in part, by the use of more refined age categories (eg., 5 year age intervals in adults). However, when this procedure is employed with skeletal samples that are derived from small anthropological populations an additional problem is introduced. Thus, the combined effects of small subsample sizes and low lesion frequencies that characterize various age/sex categories will give rise to unstable, or spurious, lesion frequencies that are of limited inferential utility.

The problems described above can be overcome by the use of macrosamples. Here, the age and sex specific skeletal lesion frequencies that are observed for two or more groups are combined. Although between group differences in skeletal lesion frequency will be masked, the macrosample summary data will more clearly identify the age and sex specific lesion patterns that are common to all human groups. The latter permit the skeletal biologist to infer probable cause of a disorder with greater confidence.

Data which summarize the age and sex specific frequency of occurrence for porotic hyperostosis in the combined Libben and Bt-5 macrosample are given in Tables 14 and 15.

TABLE 14. *Age-Specific Frequency of Occurrence for Porotic Hyperostosis in the Combined Sample of Libben and Bt-5 Subadults (0-15 years)*

		Unremodeled Lesions		Remodeled Lesions		Total Lesions		Extra-orbital Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_5	(%)
0.0 - 0.5	99	0	0.0	0	0.0	0	0.0	0	0.0
0.5 - 1.0	55	13	23.6	0	0.0	13	23.6	9	16.4
1.0 - 3.0	85	52	61.2	7	8.2	59	69.4	18	21.2
3.0 - 5.0	36	9	25.0	10	27.8	19	52.8	2	5.6
5.0 -10.0	63	15	23.8	20	31.8	35	55.6	5	7.9
10.0 -15.0	72	19	26.4	12	16.7	31	43.1	1	2.8
Total	410	108	26.3	49	12.0	157	38.3	36	8.8

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, total number of specimens that were scored positive for remodeled and/or unremodeled lesions per age group; n_5, number of specimens that manifested extra-orbital lesions per age group.

TABLE 15. *Age-Specific Frequency of Occurrence Porotic Hyperostosis Among the Combined Libben and Bt-5 Adult Samples*

	Female							*Male*						
		Unremodeled Lesions		Remodeled Lesions		Total Lesions			Unremodeled Lesions		Remodeled Lesions		Total Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_1	n_2	(%)	n_3	(%)	n_4	(%)
15 - 19	27	7	25.9	8	29.6	15	55.6	26	1	3.9	4	15.4	5	19.2
20 - 24	25	7	28.0	4	16.0	11	44.0	30	1	3.3	4	13.3	5	16.6
25 - 29	27	3	11.1	5	18.5	8	29.6	29	1	3.5	5	17.2	6	20.7
30 - 34	24	1	4.2	4	16.7	5	20.8	42	0	0.0	7	16.7	7	16.7
35 - 39	24	2	8.3	5	20.8	7	29.2	37	1	2.7	3	8.1	4	10.8
40 - 44	33	2	6.1	8	24.2	10	30.3	19	0	0.0	1	5.3	1	5.3
45 - 49	21	3	14.3	1	4.8	4	19.1	14	1	7.1	1	7.1	2	7.3
+50	28	3	10.7	3	10.7	6	21.4	11	0	0.0	1	9.1	1	9.1
Total	209	28	13.4	38	18.2	66	31.6	209	5	2.4	26	12.1	31	14.9

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, total number of specimens that were scored positive for remodeled or unremodeled lesions per age group.

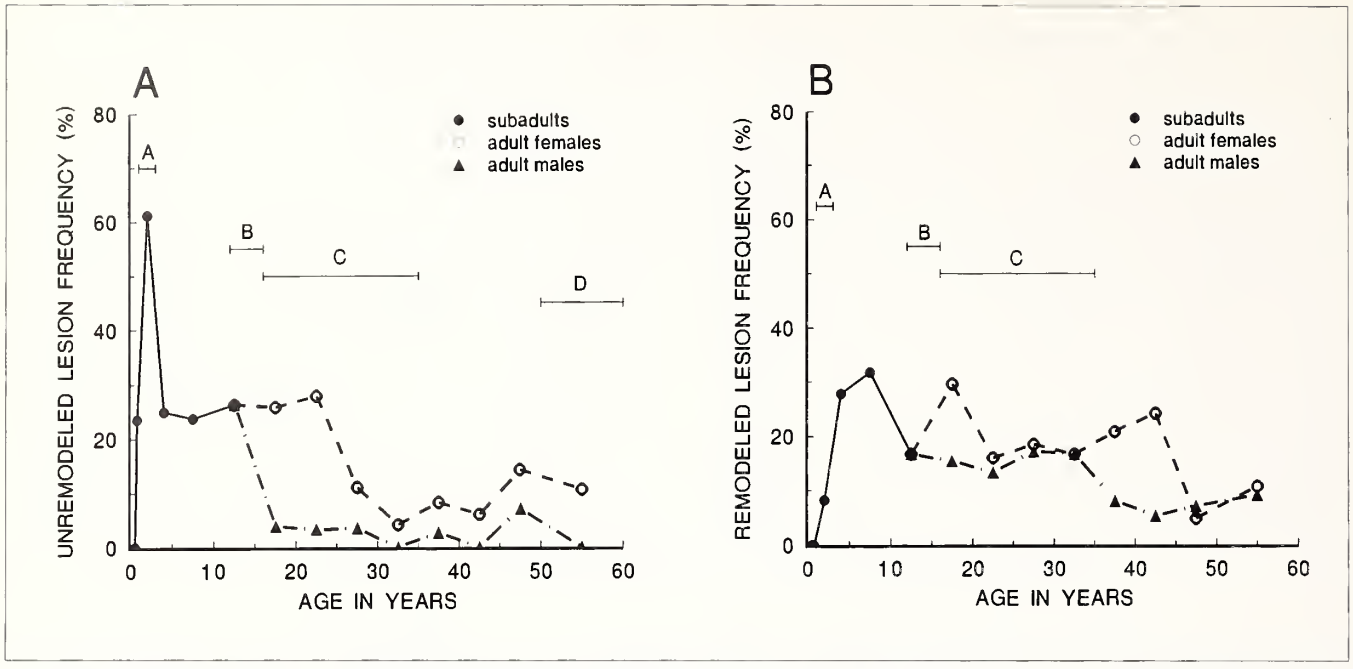

FIGURE 7. *Libben and Bt-5 combined macrosample age specific frequencies of occurrence for* (7a) *unremodeled and* (7b) *remodeled porotic hyperostosis.*

The age and sex specific frequency distributions for unremodeled and remodeled lesions in the macrosample are illustrated in Figures 7a and 7b, respectively. The ages at onset, peak incidence, and remission for unremodeled lesions that characterize the macrosample are similar to those that were described earlier for each group. Thus, peak frequencies for unremodeled lesions occurred in young children one to three years of age, and adult females 15 to 25 years of age at time of death. In addition, adolescents and adults over 45 years of age showed slight, but insignificant, increases in the frequency of unremodeled lesions. However, adult males showed a low incidence of active lesions at all ages. Thus, age and sex related macrosample patterns for unremodeled lesions identify those age/sex groups of a population at highest risk of acquiring iron deficiency. Moreover, these patterns exhibit a marked concordance with the hypothetical model of unremodeled porotic hyperostosis lesion frequencies that would be expected as a result of iron deficiency alone (see Figure 3a).

The ages at onset, peak incidence, and remission for remodeled lesion frequencies in the Libben and Bt-5 macrosample also conform to the pattern that would be expected to occur in association with iron deficiency anemia. Figure 7b clearly shows that remodeled lesion frequencies display a lag phase which translates to the right of each high risk age/sex group. These patterns are concordant with those established in the hypothetical model illustrated in Figure 3c. Macrosample data given in Table 13 also show that young adult females 15 to 30 years of age have a frequency of unremodeled porotic hyperostosis which is 13 percent higher than adult females over 30 years of age at death. A chi square comparison indicates that this difference is statistically significant (χ^2=7.22; p<.01). Thus, the age-related frequency distribution for unremodeled porotic hyperostosis in adult females identifies those individuals at greatest risk of acquiring iron deficiency anemia during the peak years of reproductive activity.

Results that have been presented thus far can be summarized as follows:

1) The vast majority of porotic hyperostotic lesions that were observed in the Libben and Bt-5 groups consisted of slight bony involvements that were primarily restricted to the superior orbital plates. Extra-orbital lesions, and lesions of moderate expression, were most commonly seen in subadults that were six months to three years of age at time of death in each group.

2) Patterns in the ages at onset, peak incidence, and remission for unremodeled porotic hyperostosis were similar in the two groups such that;

   a) the highest frequency of unremodeled lesions occurred in subadults,
   b) adult females showed the second highest frequency of unremodeled lesions at time of death, and

c) adult males showed the lowest incidence of unremodeled lesions.

3) Within group comparisons indicated that;

a) subadults in each group experienced a significantly greater frequency of unremodeled lesions compared to adult males, and Libben subadults also displayed a significantly greater frequeney of unremodeled lesions compared to adult females,
b) adult females in each group exhibited unremodeled lesion frequencies that were significantly greater compared to adult males, and
c) young adult females that were 15 to 30 years of age showed a greater frequency of unremodeled lesions compared to females over 30 years of age in each group. However. this difference was only significant for the Libben adult female eomparison.

4) Unremodeled and remodeled porotic hyperostosis frequency data for the Libben and Bt-5 macrosample indicate a marked concordance with the hypothetical iron deficiency anemia model. Thus, age and sex specific patterns in the frequency of occurrence for porotic hyperostosis clearly identify those age/sex groups at greatest risk of acquiring iron deficiency anemia in human groups.

5) Between group comparisons showed that:

a) unremodeled lesion frequencies that were observed in Libben and Bt-5 adult males, and adult females, were similar in magnitude, and
b) the only significant difference in the frequency of porotic hyperostosis that characterized the two groups was confined to subadults. Here, Libben children displayed a significantly greater frequency of unremodeled and total lesions compared to Bt-5 subadults.

Discussion

Level of Non-Specificity and Differential Diagnosis for Porotic Hyperostosis

With regard to level of non-specificity, it must be emphasized that disease prevalence differentials enhance our ability to infer the probable cause of porotic hyperostosis with a high degree of confidence on a populational basis. For example, due to their rare occurrence in small anthropological populations, many of the conditions which promote erythroid marrow hyperplasia (see Table 1) could have played little or no singular, or collective, role in the etiology of the lesion (eg., hereditary spherocytosis, congenital nonspherocytic anemias, etc). Iron deficiency anemia and the congenital hemolytic anemias are the only disorders that are sufficiently prevalent to account for the frequency with which porotic hyperostosis occurred in earlier human groups. In addition, the congenital hemolytic anemias can only be invoked to explain frequency of the lesion in certain geographically restricted populations in the Old World. Regardless, the view posited here is that porotic hyperostosis, as a bioassay of population fitness, is characterized by a very low level of non-speeificity relative to most other non-specific indicators of disease and nutritional stress.

The various pathological skeletal changes that occur in response to the anemias, and which aid in the differential diagnosis thereof, have been thoroughly investigated by Moseley (1965, 1966, 1974). His observations, combined with the age and sex related patterns reported here, served as the basis for evaluating the pathogenesis of Libben and Bt-5 porotic hyperostosis. The skeletal remains of all Libben and Bt-5 individuals were therefore surveyed for pathological changes known to occur in iron deficiency anemia and the congenital hemolytic anemias (i.e., sickle cell anemia and thalassemia) (Moseley, 1975). For reasons discussed above, other conditions were excluded from consideration.

Skeletal changes in the skull that are produced by erythroid marrow hyperplasia were described earlier. Those that are observed most frequently affecting the long bones include (1) widening of the marrow spaces, (2) cortical thinning, and (3) coarsening of trabecular patterns (Angel, 1967; Moseley, 1974). However, these skeletal changes occur in response to the hemolytic anemias, iron deficiency anemia, and are also known to accompany a wide variety of other disease and nutritional disorders (Jaffe, 1972; Aegerter and Kirkpatrick, 1975; Greenfield, 1975). These pathological changes are therefore highly non-specific and of little diagnostic utility.

Here, it should be emphasized that skeletal changes other than those produced by marrow hyperplasia are more important for diagnosis of the hemolytic anemias. For example, *vertebral step deformity* and *hand-foot syndrome* are the most reliable skeletal criteria for the identification of sickle cell anemia (Moseley, 1974). Also, children with sickle cell anemia often exhibit bone infarctions, osteomyelitis, and periostitis (Jaffe, 1972). However, it is well known that infants and young children are at greater risk of acquiring bone infections compared to older individuals (Robbins, 1974). Furthermore, periosteal reactions can be induced by a wide variety of disease agents (Greenfield, 1975). Therefore, the latter types of skeletal lesions cannot be regarded as diagnostic for the hemolytic anemias.

In other circumstances, the extent of bone marrow proliferation is a more important indicator as to the nature of the underlying anemic stimulus. Studies concerned with the biodynamics of marrow response to anemia have shown that bone marrow proliferation is dependent on the amount

of iron available to the tissue (Hillman and Henderson, 1969; Hillman, 1970). For example, the level of erythroid marrow hyperplasia that occurs in iron deficiency anemia is usually self-limiting and generally approximates only 2 to 3 times the normal rate (Finch, 1970). In severe chronic iron deficiency anemia bone marrow proliferation may on occasion reach levels that are 4 to 6 times normal (Giblett *et al.*, 1950; Hillman and Henderson, 1969). In contrast, individuals suffering from hemolytic anemias frequently exhibit a marrow response that is 5 to 10 times above normal which then results in excessive hypertrophic bony changes in the skull (Finch, 1970; Moseley, 1974).

Moseley (1974) has remarked that the skeletal changes due to marrow hyperplasia which occur in thalassemic homozygotes are more pronounced than those found in any other condition. Facial bones are often involved to the extent that malocclusion and a *rodent facies deformity* become manifest. The most reliable post-cranial skeletal change that has been observed in thalassemic homozygotes is bulbous expansion of the ribs. This primarily affects the posterior portions of the ribs and represents an exaggerated response to subperiosteal bone marrow proliferation (Moseley, 1974). Thus, the excessive levels of marrow proliferation which occur in the hemolytic anemias are determined, in part, by the increased amount of bioavailable iron that is retrieved from lysed red blood cells (Smith, 1972). None of the skeletal changes that are considered pathognomonic for the hemolytic anemias were observed in any Libben or Bt-5 individuals. The overwhelming majority of porotic hyperostotic lesions that were seen in the two groups involved only slight degrees of osseous tissue hypertrophy. These findings suggest that most Libben and Bt-5 individuals with porotic hyperostosis experienced a limited level of marrow hyperplasia which is similar to that reported in acute iron deficiency anemia. This is in contrast to the pronounced skeletal changes that would be expected to occur in greater frequency as a result of severe chronic iron deficiency anemia or the hemolytic anemias.

It is concluded here that (1) the marked age and sex specific frequency distributions for the lesion, (2) the absence of skeletal changes that are considered pathognomonie for the hemolytic anemias, and (3) the low levels of osseous tissue response that were observed, support the inference that the majority of porotic hyperostosis in the Libben and Bt-5 skeletal groups was the result of acute iron deficiency anemia.

Age and Sex Related Demographic Sensitivity of Porotic Hyperostosis

Mortality data reported earlier show that no significant differences characterize between group comparisons of Libben and Bt-5 adult survivorship. Similarly, no significant differences were observed for between group comparisons of Libben and Bt-5 porotic hyperostosis frequency in adults. These results held true for both sex-combined and sex-specific intergroup comparisons of mortality and lesion frequency data. Therefore, the demographic and paleoepidemiological patterns that were observed for adults in the two skeletal groups display a marked concordance.

Even though adult survivorship distributions were not substantially different for comparisons within or between each group, the average Libben:Bt-5 adult q_x ratio of 1.24 shows a slight trend favoring higher age-specific mortality rates in Libben adults.[5] Similarly, the Libben:Bt-5 adult sex-combined porotic hyperostosis ratios for the frequency of unremodeled and total lesions are 1.09 and 1.35, respectively. Therefore, the minor between group differences in the frequency of porotic hyperostosis correspond in direction, though not necessarily in magnitude, to the minor difference in mortality rates that characterize Libben and Bt-5 adults. Within group comparisons of adult male versus female porotic hyperostosis showed that Libben and Bt-5 females both had a significantly greater frequency of unremodeled lesions at time of death. The Libben adult female:male porotic hyperostosis frequency ratios for unremodeled lesions are 6.50 and 4.21, respectively. Comparable sex ratios for total lesions at Libben and Bt-5 are 2.19 and 1.97, respectively.

The sex-related lesion frequency differences described above would prompt some skeletal biologists to suggest that elevated pregnancy and lactation stress would result in higher levels of morbidity and mortality in adult females. However, it is unwise to base such conclusions on skeletal lesion frequency data alone. It was previously stated that no significant differences characterize patterns of adult male and female survivorship in each group. Indeed, Libben and Bt-5 adult females displayed a trend where age-specific survivorship either equaled, or exceeded, that of males in each series. Given that factors involved in the risks of acquiring iron deficiency anemia differ markedly for adult males and females, the finding that Libben and Bt-5 females displayed a significantly greater frequency of unremodeled lesions is not unexpected. However, it is clear that these sex-related differences in the frequency of porotie hyperostosis are demographically insensitive. Therefore, while sex-related differences in the frequency of the skeletal lesion may be of value for purposes of differential diagnosis, they do not appear to provide useful information about Libben and Bt-5 adult sex-specific mortality experience.

Information reported earlier shows that the only significant differences between Libben and Bt-5 porotic hyperostosis frequencies and demographic parameters are confined to subadults. That is, (1) Libben children displayed a significantly greater frequency of unremodeled and total porotic hyperostotic lesions at time of death, and (2) significantly fewer Libben individuals survived to age

15 compared to Bt-5 subadults. These results indicate the frequency of porotic hyperostosis in subadults and survivorship at age 15 are inversely related in the two groups.

With regard to demographic sensitivity, the additional findings are of interest. The Libben:Bt-5 subadult porotic hyperostosis ratios for the frequency of unremodeled and total lesions are 2.18 and 1.88, respectively. The average Libben:Bt-5 mortality ratio for subadults 0 to 15 years of age is 1.60. Differences in the frequency of Libben and Bt-5 subadult porotic hyperostosis therefore correspond in direction and magnitude to differences in subadult mortality that was observed for the two groups. Indeed, ratios that compare Libben and Bt-5 subadult lesion frequencies exceed the subadult mortality ratio and exhibit demographic hypersensitivity for individuals in this age category.

For inferential purposes, the relationships described above were formalized so that subadult porotic hyperostosis lesion frequencies could be used to predict survivorship at age 15 (l_{15}) in earlier human groups. The algorithms are presented as follows:

1a. $y = .05337(x_1) + 69.072$
$y = l_{15}$
x_1 = frequency of unremodeled porotic hyperostosis that is observed in subadults (0-15 years)

1b. $y = -0.4307(x_2) + 71.506$
$y = l_{15}$
x_2 = frequency of total porotic hyperostotic lesions that are observed in subadults (0-15 years).

Given that only two skeletal samples were used to generate the equations listed above, it is clear that the relationships posited must be regarded as hypotheses. The extent to which the models accurately reflect the relationships between porotic hyperostosis and survivorship at age 15 in earlier human groups awaits more rigorous tests that employ a substantially greater number, and temporospatial diversity, of skeletal groups. Future analyses are required to determine (a) the precision with which lesion frequencies can accurately estimate demographic parameters of earlier human groups, and (b) whether a linear or non-linear model provides the best measure of a relationship as such. Alternatively, it may be found that porotic hyperostosis lesion frequencies provide no useful information for demographic inference whatsoever. These are matters that must be addressed in future research.

Developmental Factors Which Influence Age-Related Differences in the Frequency of Occurrence and Morphological Expression of Porotic Hyperostosis

Results presented here, and elsewhere, document that children under ten years of age generally display greater frequencies and degrees of severity for porotic hyperostosis compared to adults in earlier human groups (Moseley, 1965; El-Najjar *et al.*, 1976; Lallo *et al.*, 1977). The intrinsic physiological and extrinsic environmental factors which promote risk of acquiring iron deficiency anemia in subadults, particularly those that are six months to three years of age, have been discussed. There are, in addition, developmental factors that differentially influence the extent to which subadults and adults are likely to manifest skeletal changes in response to erythroid marrow hyperplasia.

For example, the liver and spleen play a dominant role in red blood cell formation during much of the fetal period (Smith, 1972). However, shortly prior to birth these tissues quiesce. Thereafter, bone marrow cavities become the principal sites of hematopoiesis throughout life (Sodeman and Sodeman, 1974). In the infant virtually all bone marrow cavities are actively involved in red blood cell formation. This results in a circumstance where, until four years of age, a delicate balance exists between the limited bone marrow space that is available for hematopoiesis, and the bone marrow space that is required to meet the rapidly growing child's increased red blood cell requirements (Smith, 1972; Sodeman and Sodeman, 1974). By four years of age the skeleton has achieved sufficient volumetric growth to provide bone marrow space in excess of hematopoietic needs. Then, during the second decade of life the bone marrow cavities in the appendicular skeleton undergo a slow transition where active red marrow is replaced by inactive yellow marrow. By twenty years of age active red marrow in the appendicular skeleton is confined to the proximal regions of the long bones. In contrast, bones of the axial skeleton (i.e., skull, vertebrae, sternum, and ribs) remain active in red blood cell formation throughout life (Robbins, 1974; Hardesty and Weatherall, 1982).

Therefore, skeletal changes that are due to erythroid marrow hyperplasia are most likely to occur in anemic children under four years of age. This is a fundamental consequence of (a) the competitive relationship between limited supply and increased demands for active marrow space, combined with (b) the numerous constitutional and environmental factors that promote the risk of developing iron deficiency anemia at this age. Infants and young children can thus be regarded as hypersensitive to skeletal changes in the anemias.

For adults and subadults alike, it is reasonable to presume that the first tissues to respond to an anemic stimulus will be those that are already active in red blood cell formation (i.e., bones of the axial skeleton) (Smith, 1972; Sodeman and Sodeman, 1974). In contrast to young children, however, the adult appendicular skeleton provides a substantial reserve of yellow marrow that is capable of reverting to active red marrow in response to a hypoxic stimulus (Sodeman and Sodeman, 1974). Therefore, the

extent to which skeletal changes will occur in the adult cranium as a result of erythroid marrow hyperplasia depends on (1) the duration and severity of the underlying anemic condition, and (2) the rate at which appendicular bone marrow sites are recruited for compensatory red blood cell formation.

Given that substantial hematopoietic reserves are readily available to the adult, it is reasonable to suggest that skeletal changes due to erythroid marrow hyperplasia will be uncommon, or extremely limited, in these individuals. In accord with this relationship are results reported by Stuart-Macadam (1985) and results obtained herein (i.e., that Libben and Bt-5 adults displayed low frequencies of unremodeled porotic hyperostosis overall, and that such lesions were minimal bony responses to marrow proliferation). Thus, adults are best regarded as hyposensitive to skeletal changes in the anemias.

It is well recognized that porotic hyperostosis of the superior orbital plates (i.e., cribra orbitalia) is by far the most common expression of the disorder. In this study orbital lesions were observed in 97.2 percent (247/254) of all Libben and Bt-5 individuals that had either remodeled or unremodeled porotic hyperostosis. Among the small sample of individuals that had one or more extra-orbital lesions in the two groups 80.6 percent (29/36) also displayed orbital lesions at time of death. The specific reason as to why the superior orbital plates are so responsive to erythroid marrow hyperplasia has eluded functional explanation. Nonetheless, this skeletal site exhibits a marked sensitivity to bone marrow proliferation and must be considered as a superior index of the skeletal disorder. Furthermore, porotic hyperostosis affecting the superior orbital plates cannot be detected by standard clinical x-ray apparatus unless the skeletal changes are as pronounced as those shown in Figure 1. Therefore, workers who (1) restrict their definition of porotic hyperostosis to include only those skeletal lesions that are seen affecting the frontal, parietal, or occipital bones proper, and (2) attempt to identify porotic hyperostosis in the living by radiographic techniques, will grossly underestimate the frequency with which the pathological bony response occurred.

The way in which erythroid marrow hyperplasia gives rise to the morbid appearance of porotic hyperostosis as seen in the skeleton is relatively easy to comprehend. Laboratory studies have shown that tissue hypoxia initially stimulates a small number of hematopoietic stem cells to enter into an intense phase of proliferation (Till and McCulloch, 1961; Trentin, 1971). This results in a circumstance where clonal colonies of undifferentiated stem cells quickly become established in the bone marrow (Sodeman and Sodeman, 1974). Then, after a few days, these differentiate into discrete colonies or *nests* of hematopoietically active bone marrow cells.

Hyperplastic activity of discrete bone marrow cell colonies is the best explanation for the manner in which porotic hyperostotic lesions acquired their porous appearance (see Figure 1b). The degree to which osseous tissue hypertrophy accompanied such lesions was probably dependent on (1) the level of hyperplasia that was attained by discrete bone marrow cell colonies, and (2) the extent to which additional marrow space was required to accommodate cells that were actively involved in hematopoiesis.

Factors Involved in the Etiology of Iron Deficiency Anemia at Libben and Bt-5

Malabsorption syndrome as a consequence of intestinal cestodiasis is a factor which may have contributed to iron deficiency anemia in the Libben and Bt-5 groups. Parasitic tapeworm infestation is usually contracted by ingestion of raw, or under-cooked, meat or fish, and occurs in geographically widespread human populations (Robbins, 1974). Libben and Bt-5 faunal analyses deseribed earlier indicate that both groups relied heavily on seasonally available freshwater marine resources. This dependence was particularly marked for the Libben group where an abundance of freshwater fish were exploited. Thus, it is conceivable that fish tapeworm infestation (i.e., *Diphyllobothrium latum*), and subsequent intestinal malabsorption of dietary nutrients, affected some individuals in both skeletal populations.

However, epidemiological surveys in contemporary aboriginal societies have shown that microbial respiratory and gastrointestinal tract infections play a much more substantial role in precipitating, and exacerbating, nutritional crises, particularly in infants and young children (Maynard and Hammes, 1970; Jose and Welch, 1970). Although parasite loads reach higher levels in anemic and malnourished children, they generally play no major role in initiating nutritional deficiency syndromes during the early years of life (Jose and Welch, 1970). Therefore, it seems unlikely that intestinal cestodiasis was important in the etiology of iron deficiency anemia and nutritional stress in Libben and Bt-5 individuals.

Constitutional factors such as prematurity and low birthweight also probably played no substantial role in the pathogenesis of Libben and Bt-5 porotic hyperostosis in subadults for the following reasons. First, the iron deficiency anemia of prematurity would be expected to produce skeletal changes that could be seen in individuals that were three to six months of age at time of death. However, no lesions were observed in Libben or Bt-5 infants prior to six months of age. Second, premature infants in contemporary under-developed societies rarely survive the neonatal period due to the numerous physiological handicaps that these individuals experience

at birth (Levine and Gordon, 1942; Maynard and Hammes, 1970; Korones, 1976). Given that premature infants only constitute 6-12 percent of live births in human groups (Maynard and Hammes, 1970 and references therein), combined with their high risk of mortality, it is highly improbable that a sufficient number of premature infants would have survived to account for the frequencies with which porotic hyperostosis occurred in Libben and Bt-5 infants.

Similarly, diet does not appear to be a major factor in the etiology of Libben and Bt-5 porotic hyperostosis. Floral and faunal analyses indicate that resources available to the two groups provided an adequate supply of bioavailable iron. Furthermore, these resources were low in chelating agents that are known to inhibit the absorption of dietary iron. It remains likely, however, that dietary factors were to some extent involved in promoting the onset of iron deficiency anemia that occurred during the weaning period in each group. Many human societies routinely incorporate high carbohydrate gruels in the weaning diet for reasons principally related to ease of preparation, mastication, and assimilation (Gordon *et al.*, 1963; Scrimshaw and Young, 1976; Farb and Armelagos, 1980). These are usually manufactured from wild or domesticated cereal grains or other indigenous vegetable resources. In addition, the introduction of solid food items in the diet exposes the weanling to novel pathogens. The latter play a substantial role in precipitating nutritional crises and growth retardation due to recurrent episodes of acute and chronic gastrointestinal tract infections (Gordon *et al.*, 1963).

Still, there is little evidence to suggest that chronic iron deficiency anemia due to dietary inadequacy was an important epidemiological factor in the development of Libben and Bt-5 porotic hyperostosis. The dramatic decrease in the frequency of unremodeled porotic hyperostosis that was seen in subadults over three years of age, and low levels of osseous tissue response that were observed in each group, are concordant with this view. These findings are in contrast to those reported for several *maize dependent* New World skeletal groups where the incidence of porotic hyperostosis remained high throughout the childhood years, and lesions displayed more severe degrees of bony involvement (Moseley, 1965; El-Najjar *et al.*, 1976; Lallo *et al.*, 1977).

In order to more clearly evaluate the extent to which diet may have played a role in the etiology of Libben and Bt-5 subadults, lesion frequencies for these individuals were compared to those that occurred in subadults from two *maize dependent* prehistoric groups. The latter represent subsamples of the skeletal materials that were employed by El-Najjar (1976) where the relationship between diet and the frequency of occurrence for porotic hyperostosis was investigated in several New World prehistoric groups.

The Anasazi subadults (n=54) were recovered from Canyon de Chelly in northeast Arizona and are affiliated with the Basketmaker II-III cultural period that extended from 400 to 700 A.D. (El-Najjar *et al.*, 1976).[6] The Peruvian subadults (n = 70) represent a poorly documented skeletal series of prehistoric South American Indians that were recovered in the earlier part of the 20th century (El-Najjar, 1976).[7] For these individuals age at death was estimated by assessments of dental maturation and eruption status in accordance with published standards (Krogman and Iscan, 1986).

Subadults that were represented in the Anasazi and Peruvian skeletal samples ranged in age from birth to ten years. Although both skeletal series have been classified as *maize dependent*, the Anasazi group were primarily horticulturalists that supplemented dietary intake by foraging (El-Najjar *et al.*, 1976). In contrast, the Peruvian group practiced intensive agriculture where subsistence was highly dependent upon the use of domesticated cultigens (El-Najjar, 1976). For the Anasazi and Peruvian subadult samples combined, this worker observed a total frequency of porotic hyperostosis that was 75.8 percent (94/124). Similarly, frequency data reported by El-Najjar (1976) yielded a figure of 74.8 percent (80/107) for subadults in these two groups. Inter-observer error was approximately one percent. Therefore, the methods used by El-Najjar and associates (1976) to identify porotic hyperostosis were found to be highly replicable.

Data enumerating the age-specific frequencies for unremodeled, remodeled, and extra-orbital porotic hyperostosis that was observed in Anasazi and Peruvian subadults (0-10 years) is given in Table 16. Summary data which compare the total frequency for porotic hyperostosis in Bt-5, Libben, Anasazi, and Peruvian subadults that ranged in age from birth to ten years are listed in Table 17. The age-specific frequency with which unremodeled porotic hyperostosis occurred in these groups is illustrated in Figure 8. Results show that the age at onset, peak incidence, and age at remission for unremodeled lesions are markedly similar in each group. The low-to-high rank order frequency for unremodeled, total, and extraorbital lesions that were observed is Bt-5, Libben, Anasazi, and Peruvian (Table 17). Chi square values that compare the total frequencies with which porotic hyperostosis occurred in each group are listed in Table 18. Results show that (1) the frequency of total lesions and extra-orbital lesions were significantly different in each group, and (2) the *maize dependent* subadults had a significantly higher frequency of total lesions and extra-orbital lesions compared to the *non-maize dependent* Libben and Bt-5 subadults.

However, there is strong evidence to suggest that the two *maize dependent* subadult samples are demo-graphically

TABLE 16. *Age-Specific Frequency of Occurrence for Porotic Hyperostosis in Prehistoric Anasazi and Coastal Peruvian Subadults (0-10 years)*

	Anasazi							*Coastal Peruvian*						
		Unremodeled Lesions		Remodeled Lesions		Total Lesions			Unremodeled Lesions		Remodeled Lesions		Total Lesions	
Age Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_1	n_2	(%)	n_3	(%)	n_4	(%)
0.0 - 0.5	1	0	0.0	0	0.0	0	0.0	2	0	0.0	0	0.0	0	0.0
0.5 - 1.0	4	2	50.0	0	0.0	2	50.0	4	2	50.0	0	0.0	2	50.0
1.0 - 3.0	18	13	72.2	1	5.6	14	77.8	24	19	79.2	4	16.7	23	95.8
3.0 - 5.0	13	5	38.5	2	15.4	7	53.8	13	4	30.8	5	38.5	9	69.2
5.0 -10.0	18	3	16.7	10	55.6	13	72.2	27	8	29.6	16	59.3	24	88.9
Total	54	23	42.6	13	24.1	36	66.7	70	33	47.1	25	35.7	58	82.9

Symbols: n_1, total number of specimens that could be examned for the presence/absence of porotic hyperostosis per age group; n_2, number of specimens that were scored positive for unremodeled lesions per age group; n_3, number of specimens that were scored positive for remodeled lesions per age group; n_4, total number of specimens that were scored positive for remodeled or unremodeled lesions per age group.

TABLE 17. *Comparison of the Total Frequency With Which Porotic Hyperostosis Occurred Among Subadults (0-10 years) From Four Culturally and Temporospatially Diverse Skeletal Groups*

		Unremodeled Lesions		Remodeled Lesions		Total Lesions		Extra-orbital Lesions	
Skeletal Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_5	(%)
Bt-5	88	12	13.6	7	8.0	19	21.6	3	3.4
Libben	250	77	30.8	30	12.0	107	42.8	31	12.4
Anasazi	54	23	42.6	13	24.1	36	66.7	18	33.3
Peruvian	70	33	47.1	25	35.7	58	82.9	46	65.7
Total	462	145	31.4	75	16.2	220	21.2	98	21.2

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis; n_2, number of specimens that were scored positive for unremodeled lesions; n_3, number of specimens that were scored positive for remodeled lesions; n_4, total number of specimens that were scored positive for remodeled and/or unremodeled lesions; n_5, total number of specimens that exhibited extra-orbital lesions.

unsound as a result of selective recovery practices. For example, even though the state of preservation is nothing less than superb for these two groups, each skeletal collection primarily consists of isolated crania alone. That is, post-cranial materials were saved for only 22.2 percent (12/54) of Anasazi subadults and 14.3 percent (10/70) of Peruvian subadults. In addition, reference to Table 16 shows that Anasazi and Peruvian infants (0-1 year) are grossly under-represented in each group. When compared to Libben and Bt-5, where infants with a low frequency of porotic hyperostosis are present in substantial numbers, this will have the net effect of inflating lesion frequencies in the Anasazi and Peruvian samples when all individuals from birth to ten years of age are compared. Therefore, the comparisons presented earlier are biased and require adjustment before valid conclusions can be reached.

Because infants are markedly under-represented in the *maize dependent* samples, these individuals were excluded from further consideration. Adjusted summary data given in Table 19 compares the total frequency with which porotic hyperostosis was observed in Bt-5, Libben, Anasazi, and Peruvian subadults that ranged in age from one to ten years. Chi square values that compare these adjusted lesion frequencies are listed in Table 20. Most between group differences that were reported earlier are still apparent for the adjusted data. However, unremodeled and total lesion frequencies in Libben and Anasazi subadults are now quite similar. Thus, the extent to which dietary differences may have resulted in a greater frequency of porotic hyperostosis in Anasazi versus Libben subadults (i.e., the pattern that was observed for comparisons of unadjusted lesion frequencies) is now obscure. Only extraorbital lesion frequencies remain significantly different for all four subadult samples that were examined.

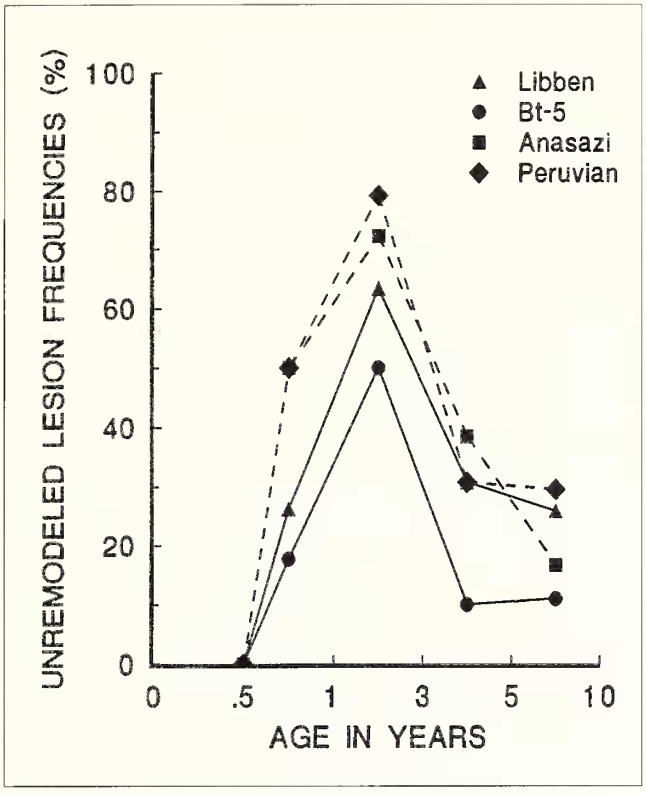

FIGURE 8. *Age-specific frequencies of unremodeled porotic hyperostosis that were observed among subadults (0-10 years) from four culturally diverse skeletal sample.*

Alternatively, it is suggested that a fundamental difference in levels of infectious disease load may have been more important in generating the subadult porotic hyperostosis frequency distributions that were observed among Libben subadults. That is, in addition to the demographic patterns reported here for the Libben and Bt-5, comparative analyses of tibia long bone growth performance, and frequency data for periosteal reactions, that were observed in subadults from these two groups, support the inference that Libben infants and children experienced higher levels of morbidity and mortality in response to elevated levels of infectious disease.

Results published elsewhere showed that Libben children six months to two years of age experienced a major period of slowed growth relative to Bt-5 (Mensforth, 1985). Growth suppression continued until four years of age when Libben children accrued a maximum 9.94 percent decrement in tibia growth relative to Bt-5. Furthermore, Libben subadults, displayed a frequencies of periosteal reactions that were significantly greater compared to Bt-5 children (χ^2=7.29; p<.01). In particular, for those ranging in age from birth to three years in particular, 51% of Libben and 27% of Bt-5 infants and young children displayed periosteal reactions (χ^2=12.24; p<.001). Among individuals affected in this age group, 79% of Libben and 65% of Bt-5 young children displayed unremodeled, or active, lesions at time of death. These skeletal lesions were interpreted to represent common microbial infections that had become established in bony tissues as a result of hematogenous seeding (Mensforth, 1986, 1985; Mensforth *et al.*, 1978).

TABLE 18. *Chi Square Values That Compare the Frequency of Occurrence for Porotic Hyperostosis in Subadults (0-10 years) From Four Culturally and Temporospatially Diverse Skeletal Groups*

		Skeletal Group		
Skeletal Group	*Lesion Status*	*Libben*	*Anasazi*	*Peruvian*
Bt-5	Unremodeled Lesions	9.88[b]	15.11[a]	21.49[a]
	Extra-orbital Lesions	5.82[c]	23.78[a]	70.74[a]
	Total Lesions	15.52[a]	28.65[a]	58.57[a]
Libben	Unremodeled Lesions		2.80	6.47[c]
	Extra-orbital Lesions		14.39[a]	85.07[a]
	Total Lesions		10.15[b]	35.13[a]
Anasazi	Unremodeled Lesions			0.25
	Extra-orbital Lesions			12.80[a]
	Total Lesions			4.36[c]

a: significant at the .001 level of probability.
b: significant at the .01 level of probability.
c: significant at the .05 level of probability.

TABLE 19. *Comparison of the Total Frequency With Which Porotic Hyperostosis Occurred Among Subadults (1-10 years) From Four Culturally and Temporospatially Diverse Skeletal Groups*

		Unremodeled Lesions		Remodeled Lesions		Total Lesions		Extra-orbital Lesions	
Skeletal Group	n_1	n_2	(%)	n_3	(%)	n_4	(%)	n_5	(%)
Bt-5	50	9	18.0	7	14.0	16	32.0	1	2.0
Libben	151	67	44.4	30	19.9	97	64.2	24	15.9
Anasazi	49	21	42.9	13	26.5	34	69.4	16	32.7
Peruvian	64	31	48.4	25	39.1	56	87.5	44	68.8
Total	314	128	40.8	75	23.9	203	64.6	85	27.1

Symbols: n_1, total number of specimens that could be examined for the presence/absence of porotic hyperostosis; n_2, number of specimens that were scored positive for unremodeled lesions; n_3, number of specimens that were scored positive for remodeled lesions; n_4, total number of specimens that were scored positive for remodeled and/or unremodeled lesions; n_5, total number of specimens that exhibited extra-orbital lesions.

TABLE 20. *Chi Square Values That Compare the Frequency of Occurrence for Porotic Hyperostosis in Subadults (1-10 years) From Four Culturally and Temporospatially Diverse Skeletal Groups*

		Skeletal Group		
Skeletal Group	*Lesion Status*	*Libben*	*Anasazi*	*Peruvian*
Bt-5	Unremodeled Lesions	11.11[a]	7.24[b]	11.42[a]
	Extra-orbital Lesions	6.66[b]	16.35[a]	52.35[a]
	Total Lesions	15.86[a]	13.84[a]	37.16[a]
Libben	Unremodeled Lesions		0.03	0.30
	Extra-orbital Lesions		6.49[c]	58.07[a]
	Total Lesions		0.43	11.85[a]
Anasazi	Unremodeled Lesions			0.35
	Extra-orbital Lesions			5.62[c]
	Total Lesions			14.52[a]

a: significant at the .001 level of probability.
b: significant at the .01 level of probability.
c: significant at the .05 level of probability.

The extent to which habitation of the Black Swamp elevated risk of acquiring infectious diseases among the Libben people remains enigmatic. Prior to being drained, in recent historic times the relatively unchanged Black Swamp was dreaded by pioneers. However, the Black Swamp acquired its reputation because it was a formidable barrier to travel and settlement (Kaatz, 1955). Thus, at least in the recent historic past, the Black Swamp has no reputation for being a source of profound human misery related to disease.

Nonetheless, a more specific scenario could be posited where we might expect aboriginal inhabitants of the rich Black Swamp to have experienced high and prolonged seasonal exposures to mosquito, and other, insect bites. Among infants and children, these circumstance alone could result in cumulative blood losses that could precipitate, or exacerbate, a latent iron deficient state. These, in turn, could easily elevate risk of microbial invasion. The latter would occur either by direct introduction of pathogens at the time when a blood meal is being secured, or indirectly as a consequence of skin irritation and inflammation. In these

ways, pathogens which normally colonize the skin and maintain a symbiotic relationship, such as *Staphylococcus aureus*, experience greater opportunities for capillary invasion and hematogenous seeding of the host. Alternatively, food preparation techniques, or the selective lack thereof, may have promoted a greater frequency, intensity, and duration of gastrointestinal tract infections in Libben infants and children.

While neither of the hypotheses presented above, either alone or in combination, can be accepted or refuted, skeletal evidence presently available favors the former relationship. That is, the majority of periosteal reactions observed in Libben subadults (1) occurred in individuals under three years of age (51% affected), (2) the highest frequency characterized infants that died in the first year of life (57% affected), (3) patterns of skeletal involvement clearly indicate that the majority of affected individuals suffered from a systemic blood-borne infectious disease, and (4) the infectious disease episodes suffered by affected individuals persisted for periods of time sufficient to elicit a frank bony response to the underlying stress episode (Mensforth *et al.*, 1978; Mensforth, 1986).

Although specific agents involved in the etiology of Libben and Bt-5 porotic hyperostosis and periosteal reactions remain speculative, the strong synergistic relationships between iron deficiency anemia and infectious disease discussed earlier cannot be ignored (i.e., impaired immune response, hypoferremia, and malabsorption syndrome). Comparative population studies have repeatedly demonstrated that infections, primarily those of the respiratory and gastrointestinal tracts, have a negative influence on hemoglobin status and play a fundamental role in precipitating nutritional crises such as iron deficiency anemia (Maynard and Hammes, 1970; Jose and Welch, 1970; Kaplan *et al.*, 1973; Burks *et al.*, 1976). These effects are most pronounced in children under three years of age where infectious disease and nutritional deficiency commonly results in the *pneumonia-weanling diarrhea syndrome* (Gordon *et al.*, 1963). The synergistic consequences of anemia and infection in contemporary underdeveloped societies are elevated morbidity, mortality, and early onset of growth retardation (Maynard and Hammes, 1970; Jose and Welch, 1970; Burks *et al.*, 1976).

The extent to which increased population densities and degrees of sedentism may have resulted in a greater prevalence of microbial and parasitic infectious diseases, nutritional deficiencies, and growth retardation in the Anasazi and Peruvian skeletal groups cannot be assessed. This is due to the fact that these samples lack suitable demographic documentation and are further characterized by infant under-representation and poor recovery of post-cranial skeletal materials. However, Kent (1987) has recently reported a case study where it is cogently argued that higher population densities, greater sedentism, and elevated levels of infectious disease may have played a more substantial role than *maize diet* in the etiology of porotic hyperostosis in prehistoric Anasazi populations.

For purposes of demographic inference, algorithms Ia and Ib were modified so that Libben and Bt-5 porotic hyperostosis frequencies adjusted for the one to ten year subadult age period could be used to predict survivorship at age 15 (l_{15}) for the Anasazi and Peruvian groups. These equations are as follows:

2a. $y = -0.3295(x_1) + 67.532$
$y = l_{15}$
$x_1 =$ unremodeled porotic hyperostosis frequency that is observed in subadults (1-10 years)

2b. $y = 0.2702(x_2) + 70.246$
$y = l_{15}$
$x_2 =$ total porotic hyperostosis frequency that is observed in subadults (1-10 years)

These algorithms predict average values for survivorship at age 15 in the Anasazi and Peruvian groups which should approximate 52.5 + 1.3 and 49.1 + 3.5, respectively. The degree to which porotic hyperostosis lesion frequencies accurately reflect these demographic projections will await further investigations of these two groups that employ sound demographic data. Finally, reference to Tables 19 and 20 show that extraorbital porotic hyperostotic lesion frequencies were significantly different for comparisons of all four subadult skeletal samples. Indeed, it was found that extra-orbital lesions accumulated at an exponential rate relative to increments in total lesion frequencies that were observed in band level foragers and *maize dependent* subadults. This relationship can be expressed as follows:

$$y = e^{ax} - 1$$

y = extra-orbital lesion frequency predicted
x = total porotic hyperostosis frequency observed
e = 2.7182818
a = .04721

The low-to-high rank order frequencies for extra-orbital lesions are Bt-5 (2.0%), Libben (15.9%), Anasazi (32.7%), and Peruvian (68.8%). These figures suggest that maize utilization by the Anasazi and Peruvian groups, combined with higher levels of population density and degree of sedentism, resulted in a greater duration and severity of iron deficiency anemia compared to the Libben and Bt-5 skeletal populations. Moreover, it is most probable that endemic hookworm disease played a substantial role in the etiology of chronic iron deficiency anemia seen in Peruvian infants and children.

With regard to porotic hyperostosis, the view posited here is that extra-orbital lesion frequencies may provide a superior skeletal index of the extent to which chronic iron deficiency anemia was prevalent in earlier human groups. As such, a useful index as such can be calculated by dividing the frequency of extra-orbital lesions observed by the frequency of total lesions observed. For the subadult skeletal samples described above these ratios are as follows: Bt-5, 0.06; Libben, 0.25; Anasazi, 0.47; Peruvian, 0.79. The benefit of this measure is its ability to detect the presence of chronic or protracted episodes of erythroid marrow hyperplasia regardless of whether total lesion frequencies are low, moderate, or high in skeletal samples under investigation.

Summary and Conclusions

The age and sex related frequencies with which porotic hyperostosis occurred in the Libben Late Woodland (n=580) and Bt-5 Late Arehaic (n=247) skeletal populations were examined. The goals of the study were to (1) identify those factors which were important in the etiology of the skeletal lesions that were observed in each group, and (2) evaluate the extent to which porotic hyperostosis serves as a useful bioassay of disease and nutritional stress in prehistoric human populations. It was suggested that stress indicators of greatest paleoepidemiological utility will be those that display high levels of biological and demographic sensitivity combined with a low level of nonspecificity.

Qualitative assessments of lesion activity status (i.e., remodeled or unremodeled) and patterns of skeletal involvement (orbital versus extra-orbital; cranial versus post-cranial, and slight, moderate, and severe degrees of bony response) were recorded for all Libben and Bt-5 individuals that displayed porotic hyperostosis at time of death. Unremodeled lesions were used to establish the age-specific frequency distributions for the lesions and identify those age/sex groups at greatest risk of acquiring the disorder. Patterns of skeletal involvement aided in differential diagnoses and served as a skeletal index of the degree to which an underlying hypoxic stimulus resulted in a greater duration and severity of the stress episode.

Results showed that the majority of Libben and Bt-5 porotic hyperostosis consisted of slight bony involvements that were restricted to the superior orbital plates of affected individuals. More pronounced degrees of osseous tissue response were somewhat more common in individuals that were six months to three years of age at time of death. No individuals in either group displayed skeletal changes that are considered diagnostic for hemolytic anemias such as sickle cell anemia or thalassemia.

Within group comparisons for broad age/sex categories showed that (a) subadults had a significantly greater frequency of unremodeled lesions compared to adults, (b) adult females had a significantly higher frequency of unremodeled lesions compared to adult males, and (c) young adult females had a greater incidence of unremodeled lesions compared to females over 30 years of age. However, the latter difference was only significant for the Libben group.

Patterns in the ages at onset, peak incidence, and remission for unremodeled and remodeled porotic hyperostosis were similar in the two groups. These data differed in no substantial way from patterns predicted by the hypothetical iron deficiency anemia related porotic hyperostosis model that was presented. Indeed, Libben and Bt-5 age and sex specific frequency distributions for unremodeled porotic hyperostosis clearly identified those age/sex groups at greatest risk of acquiring iron deficiency anemia as a result of intrinsic physiological and extrinsic environmental risk factors.

Sex-specific between group comparisons showed that Libben and Bt-5 adult males, and adult females, displayed similar frequencies of porotic hyperostosis. The only substantial difference that was observed between the two groups was confined to subadults where Libben children displayed a significantly greater frequency of unremodeled and total lesions compared to Bt-5 children.

Compared to most other conditions that promote erythroid marrow hyperplasia, only iron deficiency anemia and/or the congenital hemolytic anemias (i.e., sickle cell anemia or thalassemia) are sufficiently prevalent to account for the frequencies with which porotic hyperostosis has been observed in earlier human groups. Therefore, it was concluded that porotic hyperostosis is characterized by a very low level of non-specificity relative to most other skeletal indicators of disease and nutritional stress.

Comparisons of Libben and Bt-5 average mortality ratios and porotic hyperostosis frequency ratios for subadults, and adults (sex-combined), were directionally concordant. Thus, porotic hyperostosis exhibits demographic sensitivity as a bioassay of health conditions for the two groups. The only exception to this was that sex ratios for adult lesions frequencies did not conform to the patterns of adult male and female survivorship that characterized each group. That is, mortality rates were approximately equal for the sexes in each group whereas adult female: male lesion frequency ratios were skewed. Therefore, it was concluded that porotic hyperostosis is demographically insensitive as an indicator of differential mortality experience in adult males and females.

Infants and young children from six months to four years of age were found to be hypersensitive to skeletal changes in the anemias. This appears to be a primary consequence of the age-specific competitive relationship between limited supply and increased demands for active marrow space, combined with numerous constitutional and environmental factors that elevate risk of developing iron deficiency

anemia in very young individuals. In contrast, adults are regarded as hyposensitive to skeletal changes in the anemias due to the faet that substantial hematopoietic bone marrow reserves are available to these individuals. Thus, porotic hyperostosis exhibits a biological sensitivity that bears a strong relationship with developmental age.

The epidemiological patterns that were observed for Libben and Bt-5 porotic hyperostosis support the interpretation that iron deficiency anemia was the primary, if not sole, cause of the skeletal lesion in these two groups. With regard to etiology, however, the following circumstances must be emphasized. Floral and faunal analyses indicate that both band level societies exploited a diverse abundance of local dietary resources. Moreover, no subadults or adults in either group exhibit skeletal evidence to suggest that chronic malnutrition owing to dietary inadequacy was a major factor influencing health status. Therefore, diet probably played a very minor role in the etiology of porotic hyperostosis at Libben and Bt-5. Similarly, evidence from contemporary epidemiological surveys suggests that parasitism played no significant role in precipitating nutritional crises in these earlier human groups.

Aside from cultural affiliations and temporospatial distributions, the principal difference between the Libben and Bt-5 skeletal samples concerns the fact that levels of subadult mortality were substantially greater. Here, it is suggested that local environmmental circumstances associated with the habitation and exploitation of the Black Swamp may have played a fundamental role in elevating infectious disease loads which resulted in a greater prevalence of iron deficiency anemia in Libben children. The strong synergistic relationships between iron deficiency anemia and infectious disease are known to have their greatest impact on patterns of infant and child morbidity, mortality, and growth performance. Moreover, these relationships are concordant with the findings that Libben subadults experienced greater frequencies of porotic hyperostosis, periosteal reactions, and an early onset of long bone growth retardation compared to Bt-5 children.

Given that subadults exhibit a marked biological and demographic sensitivity to erythroid marrow hyperplasia (1) algorithms were presented whereby subadult porotic hyperostosis frequencies can be used to predict survivorship at age 15 in earlier human groups, and (2) porotic hyperostoss frequencies for Libben and Bt-5 subadults were eompared to those observed in two prehistorie *maize dependent* skeletal samples. When the latter comparisons were restricted to the one to ten year age interval, in order to adjust for infant under-representation in the Anasazi and Peruvian samples, it was found that Libben and Anasazi subadults had similar frequencies of unremodeled and total lesions. These findings suggest that similarities in degree of sedentism and population density may be responsible for the similarity in lesion frequencies that were observed. Alternatively, it is suggested that increased sedentism, population density, and high levels of endemic hookworm infestation contributed to the elevated frequency of porotic hyperostosis that characterizes the sample of Peruvian subadults.

In contrast, the frequency with which extra-orbital porotic hyperostosis occurred was significantly different in all four subadult samples that were examined. It was found that extra-orbital lesions accumulate at an exponential rate relative to total lesions, and may therefore provide a superior skeletal index of the extent to which chronic iron deficiency anemia occurred in earlier human groups. The greater prevalence of extra-orbital lesions in the *maize dependent* subadult samples may reflect the extent to which dietary inadequacy promoted a greater duration and severity of iron deficiency anemia in these groups.

Finally, it is interesting that few investigators concerned with the pathogenesis of porotic hyperostosis in Old World skeletal groups have seriously entertained the iron deficiency anemia hypothesis (for exceptions see Hengen, 1971 and Carlson *et al.*, 1974). This is particularly true for researchers who have been concerned with the etiology of the lesion in circum-mediterranean skeletal groups (Angel, 1967; Ascenzi and Salistreri, 1977; and Germana and Ascenzi, 1980). Given the fact that iron deficiency anemia is prevalent throughout the world (Witts, 1966), particularly in agricultural communities (World Health Organization, 1968), it is clear that the *iron deficiency* and *hemolytic* anemia hypotheses cannot reasonably be considered as mutually exclusive explanations for the occurrence of porotic hyperostosis in Old World circum-mediterranean skeletal populations. It is highly improbable that those human groups subjected to the selection pressures of falciparum malaria would be uniquely exempt from basic human, and mammalian, pathophysiological responses to disease and nutritional stress. Likewise, the iron deficiency and hemolytic anemia hypotheses cannot reasonably be invoked to explain the occurrence of the skeletal lesion on a discrete continental basis as has been suggested (Angel, 1967). Thus, many studies that have investigated the pathogenesis of porotic hyperostosis in Old World prehistoric groups are clearly in need of substantial revision.

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Notes

1. The Libben site skeletal materials are permanently curated by the Department of Sociology and Anthropology at Kent State University, Kent, Ohio.

2. The Carlston Annis Bt-5 site skeletal materials are permanently curated by the Department of Anthropology at the University of Kentucky, Lexington.

3. The criterion that was used to identify lesions of minimal expression conform to those employed by El-Najjar *et al.* (1976) where one or more clusters of pores which extended 5 millimeters in diameter or greater were considered as indicating presence of the lesion. Lesions of moderate expression typically involved a greater surface area of the affected bone, displayed a well-developed cribriform mesh, and usually exhibited clearly discernable osseous tissue hypertrophy. Lesions of severe expression were interpreted to represent skeletal changes that were associated with extensive osseous tissue hypertrophy, marked expansion of diploic spaces, and commonly involved the frontal, parietal, and occipital bones in combination with the superior orbital plates.

4. In the present study porotic hyperostotic lesions were simply classified as orbital or extra-orbital with respect to cranial bones affected. Other workers have suggested lesion typologies based on physical appearance of the lesion or the anatomical disposition of the lesion in the skull. For example, Nathan and Haas (1966) described orbital porotic hyperostosis as being porotic, cribrotic, or trabeculated in appearanee. Carlson and associates (1974) have alternatively suggested that lesions be classified as cribra orbitalia, spongy hyperostosis, and osteoporotic pitting. These descriptive terms were not used in the present study because they primarily reflect degree of osseous tissue response and no further pathophysiological significance can be attributed to the use of such jargon. Thus, the terminology employed here corresponds with that currently advocated by several researchers who have directed their long term efforts toward developing a bettern comprehension of the nature and significance of porotic hyperostosis in earlier human groups (G. J. Armelagos, personal communication).

5. Age-specific Libben:Bt-5 q_x ratios are listed in Table 2. The average Libben:Bt-5 q_x ratios for adults and subadults were estimated by calculating the mean for all q_x ratios that were observed for each age group. The values for adults (+15 years) and subadults (0-15 years) are 1.24 and 1.60, respectively.

6. The Anasazi skeletal materials are permanently curated by the American Museum of Natural History, New York.

7. The Peruvian skeletal materials are permanently curated by the Chicago Field Museum, Illinois.

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